ANESTHESIOLOGY

The Journal of

The American Society of Anesthesiologists, Inc.

MAY, 1947

Volume 8 Number 3

ANESTHESIOLOGY

THE JOURNAL OF

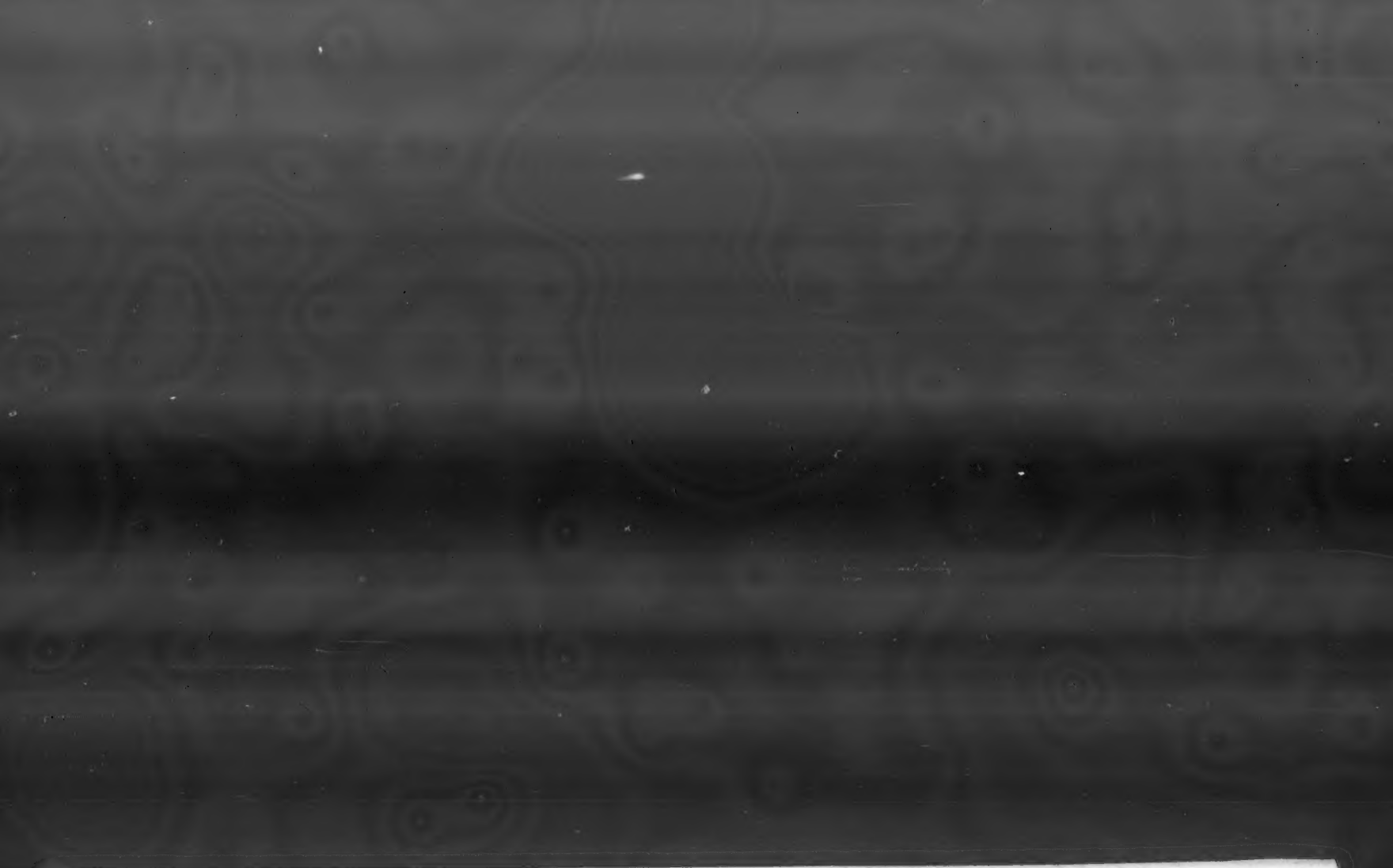
THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

Published bi-monthly at Prince and Lemon Streets, Lancaster, Pa., by The American Society of Anesthesiologists, Inc. Copyright, 1947, by The American Society of Anesthesiologists, Inc., New York, N. Y. Printed in United States of America. Subscription rates per annum, in advance, including postage:

Domestic, $6.00; Canadian, $6.50; Foreign, $7.00.

Entered as second-class matter July 2, 1940, at the post-office at Lancaster, Pennsylvania, under the Act of August 24, 1912.

BUSINESS EDITOR, FREDERICK P. HAUGEN, M.D.
51 N. 39th St., Phila. 4, Pa.



ANESTHESIOLOGY

The Journal of

THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

Volume 8 MAY, 1947 Number 3

GASEOUS ANAESTHETICS *

WESLEY BOURNE, M.D.

Montreal, Canada

Received for publication November 5, 1946

THE father of pneumatic chemistry lived in a great age, an age remarkable for great names, which recall to mind great ideas. Johnson, Voltaire, Swift, Rousseau, Washington, Franklin, Goethe, Napoleon, Nelson, Pitt, and many other leaders lived in the same age as Priestley What pictures such names conjure! At that time, from his Virginian mountaintop, the sage of Monticello surveyed the Blue Ridge twenty miles away, while glancing through his telescope, year after year, in the other direction, he watched the rising of the walls of Charlottesville. Thomas Jefferson was very considerate of Joseph Priestley, consulted him about the new university and showed him several marks of intimate friendship. "In England, as a young man, Priestley had fallen in with Franklin, who had given him a collection of books, while quickening his political thought, and all but started his career as an inventive chemist." Van Wyck Brooks in his *The World of Washington Irving* (1) goes on to style him: "This eighteenth-century Bertrand Russell." Before leaving England Priestley had discovered oxygen on the 1st of August 1744, calling it dephlogisticated air, and in April 1776 he prepared nitrous oxide. "Coleridge and Southey, the English poets, had planned for a while to come with Priestley, for the word Susquehanna struck Coleridge as metrical and charming. They dreamed of leaving the old world of falling thrones and rival anarchies to found a pantisocratic community there. One of them would wield an axe, one would guide a plough, and each would work for all, with possessions in common. In the woods and wilds their wants would be simple, and their offspring would be beautiful and hardy, and they hoped to create a new literature there, bathed in the spring of life and nature, that would

* Presented, by invitation, Wednesday, October 16th, 1946, *Morton Centennial*, American Society of Anesthesiologists, Inc., and New England Society of Anesthesiology, Boston, Mass.

restore the age of innocence. In the end Priestley came alone to live and die on the Susquehanna."

Coeval with Priestley was Antoine Laurent Lavoisier, *le fondateur de la chimie modèrne.* By dint of his genius there rose a *nouvelle chimie.* Lavoisier is, without doubt, the father of modern chemistry. In 1778 (the year of the death of Voltaire and of Rousseau within thirty-three days of each other) Lavoisier established the fact that oxygen was the universal oxidizing principle. During 1775 and on he expounded his views on the nature of respiration, fermentation and combustion. The late Professor Graham Lusk, in his text-book, "The Science of Nutrition," continually expressed amazement at the penetration of Lavoisier's experiments. He quoted the respiration experiments on man by Lavoisier and Seguin and stated that "these remarkable results are in strict accord with the knowledge of our own day. We know more details, but the fundamental fact that the quantity of oxygen absorbed and of carbon dioxide excreted depends primarily on (1) food, (2) work, and (3) temperature, was established by Lavoisier within a few years after his discovery that oxygen supported combustion." Lusk goes on to state: "The modern era of the science of nutrition was opened by Lavoisier in 1780. He was the first to apply the balance and the thermometer to the phenomenon of life, and he declared *'La vie est une fonction chimique.'* " One does well to consult Kerr's translation of Lavoisier's *Traité Élémentaire de Chimie* (2).

Everybody is familiar with the work of Humphry Davy (3) on nitrous oxide. The publication of the results of his researches in the Medical Pneumatic Institution at Bristol reveals extensive studies which were divided in four parts. In the Introduction he declared that "the first Research in this work chiefly relates to the production of nitrous oxide and the analysis of nitrous gas and nitrous acid. In this there is little that can be properly called mine; and if by repeating the experiments of other chemist, I have sometimes been able to make more minute observations concerning phaenomena, and to draw different conclusions, it is wholly owing to the use I have made of the instruments of investigation discovered by the illustrious fathers of chemical philosophy, and so successfully applied by them to the discovery of truth." Davy goes on to give accounts of his "Experiments and Observations on the Effects Produced upon Animals by the Respiration of Nitrous Oxide." He considers a gas as *respirable* when it can be introduced into the lungs by voluntary effort, without any relation to its power of supporting life. "*Non-respirable* gases are those, which when applied to the external organs of respiration, stimulate the muscles of the epiglottis in such a way as to keep it perfectly close on the glottis; thus preventing the smallest particle of gas from entering into the bronchia, in spite of voluntary exertions; such are carbonic acid, and acid gases in general." Of the respirable gases, "one only has the power of uniformly supporting life;—atmospheric air. Other gases, when respired, sooner or later produce death; but in different

modes." Referring to some experiments of Lavoisier and of Dr. Beddoes, Davy stated that "Oxygene, which is capable of being respired for a much greater length of time than any other gas, except common air, finally destroys life; first producing changes in the blood, connected with living action." The animals employed were cats, dogs, rabbits, guinea-pigs, hens, a goldfinch, mice; and amphibious animals, such as water-lizards; and too, fish, as flounders and thornbacks; and finally, winged insects of all sorts. The conditions of the experiments were varied and whereas several of these living things were purposely exposed long enough for them to die in order that postmortem examinations could be made, many others were removed soon enough so that they recovered completely. Davy found that animals "are capable of living for a great length of time in nitrous oxide mingled with very minute quantities of oxygene or common air."

When, in April, 1799, Davy produced nitrous oxide in a state of purity, and ascertained many of its chemical properties, he resolved to inspire it in its pure form. Accordingly, "On April 11th," he stated, "I made the first inspiration of pure nitrous oxide; it passed through the bronchia without stimulating the glottis, and produced no uneasy feeling in the lungs. The result of this experiment, proved that the gas was respirable, and induced me to believe that a farther trial of its effects might be made without danger." After this he repeated his personal experience on several occasions and made careful observations, among which one finds the following: "The power of the immediate operation of the gas in removing intense physical pain, I had a very good opportunity of ascertaining. In cutting one of the unlucky teeth called dentes sapientiae, I experienced an extensive inflammation of the gum, accompanied with great pain, . . . On the day when the inflammation was most troublesome, I breathed three large doses of nitrous oxide. The pain always diminished after the first four or five inspirations; the thrilling came on as usual, and uneasiness was for a few minutes, swallowed up in pleasure."

Davy next recounted the details of the effects produced by the breathing of nitrous oxide upon several individuals. Among these were Josiah Wedgwood and Thomas Wedgwood of china-ware fame, the poets Coleridge and Southey, Dr. Beddoes and Dr. Kinglake. This last mentioned wrote that "its agency was exerted so strongly on the brain, as progressively to suspend the senses of seeing, hearing, feeling, and ultimately the power of volition itself." Among Davy's conclusions is found that classical statement: "As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations. . . ."

In yonder time gone by, before the dawn of anaesthesia, the night was dark and long and bespangled only with lettuce, mandragora, Dionysiac potions and the *gas* evolved when vinegar was mixed with crushed stone from Memphis. But with early dawn, Aurora-like came Priestley, Lavoisier, Davy and Faraday—for Michael Faraday (4),

too, in 1818, had published his observation that the inhalation of the *vapour* of ether "produces effects very similar to those occasioned by nitrous oxide." These four philosophers of chemistry threw open the doors and showed the pathway. To us, at this far time removed, it seems strange that their suggestions were not developed more readily. It is true that Henry Hill Hickman in 1824 had convinced himself of the efficacy of carbon dioxide to suspend animation in mice and dogs sufficiently for any surgical operation. Yet he failed in his definite attempts to persuade the physicians and surgeons of England and of France to apply his discovery to practice in man, even though Sir Humphry Davy was, at the time, president of the Royal Society and Baron Larrey supported his cause. "Nevertheless, he deserves the credit of having been the first of the modern investigators to prove by experimentation on animals that the pain of surgical operation could be abolished by the inhalation of a gas (5)." It was at about this time that William Cullen Bryant abandoned the law and devoted himself to literature, and that Washington Irving was in England sharing intellectual communion with Charles Lamb, Sir Walter Scott, Samuel Taylor Coleridge, J. M. W. Turner, Charles R. Leslie and others.

It was not till the *forties,* when New England was flowering, when Oliver Wendell Holmes sang immortal songs, taught so thoroughly that he found each time that something had gone out from him, wrote inimitable books. It was not till then, and the dawn of anaesthesia was still dim, that there was, in the hands of Horace Wells, another failure to make known that a gas could produce anaesthesia effectively even though he himself had been anaesthetized for the extraction of a tooth on December 11, 1844. Although "Wells returned to Hartford and used nitrous oxide successfully in his dental practice in 1845, as the deposition of some forty respectable citizens of Hartford indicates, the use of this gas was abandoned until June, 1863, when Dr. Gardner Q. Colton revived it in New Haven, Connecticut, administering it for Dr. J. H. Smith, a distinguished dentist of that city. Although Wells had failed to convince the world of the value of nitrous oxide as an anesthetic agent, he is credited with conceiving the idea of anesthesia and publicizing the possibility of its use."

Lewis Mumford (6), the biographer, said that Herman Melville "fell in with the (ship's) doctor, who was an educated man, as naturally as one globule of mercury will coalesce with another as soon as they touch." By the summer of 1843 Melville had shipped aboard the frigate, *United States,* upon its homeward voyage. "The free, vagrant, uncertain life of the rover was over: he was in the Navy now." Melville must have had more than a dim anticipation of a career as a writer when he stepped ashore at Boston, in October, 1844.—one is reminded of the stepping ashore of Henry Adams (7), with his father, Minister to England, and with John Lothrop Motley. They stepped ashore at Boston, in July 1868—How different the circumstances! Had Melville known where it would lead him he might well have shrunk from

following it further. Mumford went on to say that "It is perhaps a little absurd to speak of such disparate things as Attica and the North Atlantic States in the same breath: but these regions, between 1820 and 1860, which coincided with Melville's birth and maturity, were in many respects in the same situation as Attica between the birth of Socrates and the death of Plato." In the World of the *forties* there was sense of ardent awaiting foretelling fulfillment. Emerson was giving his lectures on the Times; Thoreau was making his experiment at Walden Pond; Johannes Peter Müller was pioneering the work of his famous pupils, Virchow, Helmholtz, du Bois Reymond and others in Berlin; Louis Pasteur was doing his brilliant work in Paris; many thinkers on each side of the Atlantic were expressing their views and enhancing the culture, men like Longfellow and Tennyson, Carlyle and Whitman, Poe and Macaulay, Dickens, and Hawthorne. There was a galaxy of intellects heralding innovation.

This very day one hundred years ago, dawn's grey mists were dispelled and light shone on Morton as he gave ether to a man (Gilbert Abbott) in Boston. At last full morning of anaesthesia had come. I am reminded of some lines from Pushkin's poem, called ympo (Morning):

Утро

Румяной зарею
Покрылся восток.
В селе за рекою
Потух огонек.

. . . . . .
. . . . . .

Проснулися люди,
Спешат на поля.
Явилося солнце,
Ликует земля.

А. Пушкин.

TRANSLATION:

The rosy hue of morning
O'erspreads the eastern sky.
And in the hamlet o'er the stream
The lamp lights fade and die.

. . . . . .
. . . . . .

The folk from slumber wakened
Forth to the furrows run.
And Earth rejoices once again
To greet the risen Sun.

A. PUSHKIN.

(Translation versified by Professor W. D. Woodhead, Department of Classics, McGill University.)

As anaesthetists, why should we bother much about the relative value of the agents we employ? What care we that a substance be called solid, liquid or gas? May it not be that some bright young person will find a so-called solid which, when it gets into solution in the blood, will produce a state of anaesthesia to match the dreams of Waters, to exceed the desires of Griffith? After all, any anaesthetic material, put into the category of *"general"* anaesthesia, no matter its physical state, must be in solution in the blood before it affects the central nervous system, and such things as ether or chloroform must become aeriform, vaporous, or *gaseous,* before they may be inhaled. Anaesthetists care more to know physiologic principles as well as drug actions, and then to suit these, in case by case, from moment to moment. After ether and chloroform came into general vogue there was a considerable period of quiescence in anaesthesia, that is, from a spectacular point of view. But the subject was being benefitted indirectly from the works of physiologists like Claude Bernard, while John Snow was paying special attention to his experiments and to his book (8). It would seem that usefulness of a gas as an anaesthetic agent had suffered stigma, even though Andrews (9) advocated a mixture of oxygen with nitrous oxide as late as 1868, and Paul Bert demonstrated that anaesthesia could be prolonged with nitrous oxide when mixed with oxygen and given under increased barometric pressure. This was exemplified with lower animals in 1879 (10) and in man the following year (11). The development of appliances, gas machines, started by Sir Frederick Hewitt (12) in 1855, means the development of gas anaesthesia. In dentistry, the effort was concerted, particularly in the hands of C. K. Teter (1903), and of J. A. Heidbrink (1909). In medicine, we are all familiar with the names E. I. McKesson, Willis D. Gatch, Karl Connell, J. T. Gwathmey and Richard v. Foregger. Thus it was that the use of nitrous oxide became universal as it was mixed with oxygen in efficient machines and administered under all sorts of conditions in dentistry and in surgery, and we find Guedel (13) employing it in obstetrics in 1909.

Our next concern in gaseity is with ethylene. Although, as recounted by Keys (5), there were several much earlier attempts to introduce this elastic fluid into anaesthesia, it was not until 1923 that W. E. Brown (14), of Toronto, and A. B. Luckhardt with J. B. Carter (15), of Chicago; working independently, published their results on ethylene as a general anaesthetic. In no time, Isabella Herb (16) published the results of her clinical study at the Presbyterian Hospital, Chicago. Since then ethylene has been used extensively and is given in similar fashion to that of nitrous oxide. Its action is no more innocuous. Its efficacy is somewhat greater than that of nitrous oxide. With regard to these two gaseous anaesthetics, let us remind ourselves at once that they should be given along with sufficient oxygen. Abundantly it has been shown that hypoxia is not permissible. Witness

Quastel's remarks about a continuous supply of oxygen (17) to the brain, and those of Jowett (18) that a definite inhibition of respiration is produced by anaesthetic concentrations sufficient to cause narcosis. Witness, too, that it has been shown that when either of these gases is given purposely with no more than 10 per cent of oxygen, the damage done to the liver (19) is much greater than that which takes place when ether is given ordinarily. At the same time the administration of either of these two gases, even over long periods, when enough oxygen is used shows no ill-effects on the liver. The action of a drug upon the liver may be taken as indicative of its influence on function generally. The interdependence of function must always be borne in mind by the anaesthetist (20).

Nearly always innovation in anaesthesia has come from the laboratory. This time, it came from the pharmacologists, G. H. W. Lucas and V. E. Henderson, of Toronto University. In August, 1929, they reported "A new anaesthetic gas: cyclopropane" (21, 22). Further pharmacologic studies were made by Seevers, Meek, Rovenstine and Stiles at the University of Wisconsin. Cyclopropane was first administered to man, in the clinical way, by Ralph M. Waters (24), in 1930, at the University of Wisconsin, where its usefulness in anaesthesia was developed (25). For excellent accounts of this drug, one is referred to Robbins' book, *Cyclopropane Anesthesia,* published by Williams & Wilkins in 1940 and to Adriani's book, *The Chemistry of Anesthesia,* published by Charles C. Thomas in 1946. Of particular importance are the following observations: premedication increases the margin of safety in cyclopropane anaesthesia; barbiturates seem to protect the individual against the cardiac irregularities which this gas is all too likely to produce; liver damage does not appear to take place in cyclopropane anaesthesia; uterine contractions are not impeded; "during the anaesthetic period the rate and rhythm of the pulse and rate and amplitude of respiration should be watched carefully;" and, nitrogen or some other slowly-absorbed gas ought to be added to the mixture of cyclopropane and oxygen in order to keep the alveoli distended, and so lessen the likelihood of atelectasis, and in order to prevent too much oxygen from getting into the blood, which would interfere with the escape of carbon dioxide from the tissues.

With regard to the problem of having too much oxygen in the blood, it may be pointed out that as long ago as 1878 (26), Paul Bert warned that the breathing of pure oxygen at normal pressure (tension 100) cannot be long endured by warm-blooded animals, and with regard to dissolved oxygen, he said that "it is a fact of the highest interest that in the presence of this free oxygen that is simply dissolved, the inner oxidations slow up, then stop. It seems that for oxidation the tissues need borrowed oxygen, taken from the oxyhaemoglobin." Stadie, Riggs and Haugaard (27) have made an exhaustive review of the topic of oxygen poisoning, and Comroe, Dripps, Dumke and Deming (28)

have made a carefully controlled comparative study of oxygen toxicity. Although adequate oxygenation is of prime importance in most forms of anaesthesia, indeed, even in some modes of "regional" anaesthesia, such as that called "high spinal," particular attention must be paid to it when the gaseous anaesthetics are employed. In the instance of cyclopropane, however, oxygenation may be over-done.

For a long time, one of the chief hindrances to the more general application of the gaseous anaesthetics, was in their failure to produce muscular relaxation. This has been met by the perspicacity of Harold Griffith of Montreal (29). The administration of curare is now being employed in anaesthesia quite universally.

Perhaps the usefulness of the gaseous anaesthetics will long continue to be particularly suitable in dentistry. Perhaps their judicious application will long continue to supply the requirements of anaesthesia in obstetrics. Perhaps the most rational manner of employing the gaseous anaesthetics, particularly in surgery, will be, increasingly, in concinnous combination with one another and with other drugs. This is undoubtedly the procedure of many anaesthetists, and we all know that there are several methods. As examples may be mentioned "spinal" anaesthesia along with nitrous oxide-oxygen anaesthesia, and intravenous anaesthesia by one of the barbiturates along with the inhalation of cyclopropane. The gaseous anaesthetics will endure all the more on account of the endotracheal method of administration, so excellently described in the book of Noel A. Gillespie (30); and, too, on account of the carbon dioxide absorption technic, incepted by Dennis E. Jackson (31) experimentally, and applied clinically by Ralph M. Waters (32).

Let us rejoice in the lustre of anaesthesia's ineffable forenoon. Let us say with Thoreau, "Why should we not meet . . . , sometimes as *eu*peptics, to congratulate each other on the ever-glorious morning?" (Henry David Thoreau: Life Without Principle).

REFERENCES

1. Brooks, Van Wyck: The World of Washington Irving, Philadelphia, The Blakiston Company, 1945.
2. Kerr, Robert: Elements of Chemistry by Mr. Lavoisier, Edinburgh, William Creech, 1799.
3. Davy, Humphry: Researches, Chemical and Philosophical; Chiefly Concerning Nitrous Oxide, or Dephlogisticated Nitrous Air, and Its Respiration, London, J. Johnson, 1800.
4. Faraday, M.: Effects of Inhaling the Vapours of Sulphuric Ether, Quart. J. Sc. & Arts. Miscellanea (art. XVI) 4: 158, 1818.
5. Keys, Thomas E.: The History of Surgical Anesthesia, New York, Schuman's, 1945.
6. Mumford, Lewis: Herman Melville, New York, Harcourt, Brace & Co., 1929.
7. The Education of Henry Adams. An Autobiography, Chapter XVI, Cambridge, Houghton Mifflin Company, The Riverside Press, 1918.
8. Snow, John: On Chloroform and other Anesthetics: Their Action and Administration. Edited, with a Memoir of the Author, by Benjamin W. Richardson, London, John Churchill, 1858.
9. Andrews, E. W.: The Oxygen Mixture, a New Anaesthetic Combination, Chicago Med. Exam. 9: 656–661 (Nov.) 1868.

10. Bert, Paul: Sur la possibilité d'obtenir, à l'aide du protoxyde d'azote, une insensibilité de longue durée, et sur l'innocuité de cet anesthésique, Comp. rend. l'academie des Sciences 87: 728–730, 1878.
11. Ibid.: Anesthésie par le protoxyde d'azote mélangé d'oxygène et employé sous pression, Compt. rend. l'academie des Sciences 89: 132–135, 1879.
12. Hewitt, F. W.: A New Method of Administering and Economising Nitrous Oxide Gas, Lancet 1: 840–841 (May 9) 1885.
13. Guedel, A. E.: Nitrous Oxide Air Anesthesia Self Administered in Obstetrics, Indianapolis M. J. 14: 476–479 (Oct.) 1911.
14. Brown, W. E.: Preliminary Report; Experiments with Ethylene as a General Anaesthetic, Canad. M. A. J. 13: 210 (Mar.) 1923.
15. Luckhardt, A. B., and Carter, J. B.: Ethylene as a Gas Anesthetic; Preliminary Communication, J. A. M. A. 80: 1440–1442 (May 19) 1923.
16. Herb, I.: Ethylene: Notes Taken from the Clinical Records, Anesth. & Analg. 2: 230–232 (Dec.) 1923.
17. Quastel, J. H.: Respiration in the Central Nervous System, Physiol. Rev. 19: 135–183 (April) 1939.
18. Jowett, M.: The Action of Narcotics on Brain Respiration, J. Physiol. 92: 322–335 (April) 1938.
19. Rosenthal, S. M., and Bourne, Wesley: The Effect of Anesthetics on Hepatic Function, J. A. M. A. 90: 377–379 (Feb. 4) 1928.
20. Bourne, Wesley: Interdependence of Function in Anesthesia, J. A. M. A. 120: 997–999 (Nov. 28) 1942.
21. Lucas, G. H. W., and Henderson, V. E.: A New Anaesthetic Gas: Cyclopropane; a Preliminary Report, Canad. M. A. J. 21: 173–175 (Aug.) 1929.
22. Henderson, V. E., and Lucas, G. H. W.: Cyclopropane: a New Anesthetic, Anesth. & Analg. 9: 1–16 (Jan.–Feb.) 1930.
23. Seevers, M. H.; Meek, W. J.; Rovenstine, E. A., and Stiles, J. A.: A Study of Cyclopropane Anesthesia with Especial Reference to Gas Concentrations, Respiratory and Electrocardiographic Changes, J. Pharmacol. & Exper. Therap. 51: 1–17 (May) 1934.
24. Waters, R. M., and Schmidt, E. R.: Cyclopropane Anesthesia, J. A. M. A. 103: 975–983 (Sept. 29) 1934.
25. Stiles, J. A.; Neff, W. B.; Rovenstine, E. A., and Waters, R. M.: Cyclopropane as an Anesthetic Agent: a Preliminary Clinical Report, Anesth. & Analg. 12: 56–60 (Mar.–April) 1934.
26. Bert, Paul: Barometric Pressure; Researches in Experimental Physiology. Translation by M. A. Hitchcock and F. A. Hitchcock. Columbus, O., College Book Company, 1943.
27. Stadie, W. C.; Riggs, B. C., and Haugaard, N.: Oxygen Poisoning, Am. J. M. Sci. 207: 84–114 (Jan.) 1944.
28. Comroe, J. H.; Dripps, R. D.; Dumke, P. R., and Deming, M. Van N.: Oxygen Toxicity, J. A. M. A. 128: 710–717 (July 7) 1945.
29. Griffith, H. R., and Johnson, G. E.: The Use of Curare in General Anesthesia, Anesthesiology 3: 418–420 (July) 1942.
30. Gillespie, N. A.: Endotracheal Anaesthesia, Madison, University of Wisconsin Press, 1941.
31. Jackson, D. E.: A New Method for the Production of General Analgesia and Anaesthesia with a Description of the Apparatus Used, J. Lab. & Clin. Med. 1: 1–12 (Oct.) 1915.
32. Waters, R. M.: Clinical Scope and Utility of Carbon Dioxide Filtration in Inhalation Anesthesia, Anesth. & Analg. 3: 20–22 (Feb. 26) 1924.

Officers for the current year of the Anesthesia Section of the Los Angeles County Medical Society are as follows:

Chairman—Seth Sensiba.
Vice-Chairman—J. William Shuman.
Secretary-Treasurer—Francis E. Guinney.

MICRODETERMINATION OF BLOOD LEVELS OF PROCAINE HYDROCHLORIDE AFTER INTRAVENOUS INJECTION

DAVID J. GRAUBARD, M.D., RAPHAEL W. ROBERTAZZI, M.D., AND M. C. PETERSON, M.D.

New York, New York

Received for publication February 7, 1947

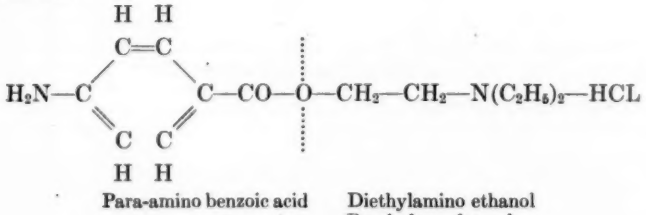
THE recently aroused interest in the use of procaine hydrochloride intravenously (1–8) has demonstrated the need for an accurate determination of blood levels of the drug. The pharmacognostics of any drug require not only a knowledge of its source, preparation, action and dosage, but also a method of determining its presence in the tissues and body fluids after its administration. Primarily, this investigation was undertaken to determine the practicability of detecting procaine in the blood stream after known amounts were injected intravenously; at the same time, some observations were made to confirm the work of others (9–11) as to the fate of procaine in the body.

A method for the determination of procaine has been described by Bandelin and Kemp (12) which is a modification of the procedure used by Bratton and Marshall (13). The method to be described is a modification of the procedure used by Bratton and Marshall for the determination of sulfanilamide in body fluids. This procedure was chosen because it is readily available for use in all laboratories and the methods described by Bratton and Marshall are already standardized. This method is applicable to procaine because the entire reaction is based upon the ability of the para-amino radicals to produce a color reaction.

In this investigation four phases of the problem of administering procaine intravenously were studied: (1) a method of determining levels of procaine hydrochloride in blood by the amount of para-aminobenzoic acid; (2) the recovery of procaine added to blood *in vitro;* (3) the stability of procaine in oxalated blood, and (4) the recovery of procaine from the blood of rabbits and human beings.

METHOD FOR DETERMINING PROCAINE HYDROCHLORIDE IN BLOOD

Procaine hydrochloride is para-aminobenzyl-diethylamino ethanol hydrochloride:



Para-amino benzoic acid Diethylamino ethanol
Break down formula

Upon diazotization the para-amino radical is produced, forming the basis for a colorimetric test. The technic of the test follows:

a. Add 1.0 cc. of oxalated blood to be tested for procaine to 15 cc. of distilled water, allowing it to lake by standing for ten minutes.

b. Add 4.0 cc. of 15 per cent trichloracetic acid; let it stand for ten minutes, and centrifuge or filter.

c. Add 1.0 cc. of 0.1 per cent sodium nitrite solution to a 10 cc. aliquot of filtrate and wait three minutes.

d. Add 1.0 cc. of 0.5 per cent ammonium sulfamate solution to the aliquot of filtrate and wait two minutes.

e. Add 1.0 cc. of a 0.1 per cent solution of N-(l-naphthyl) ethylene diamine dihydrochloride and let stand for ten minutes.

f. The standard of procaine hydrochloride should contain 0.04 mg. per cc., and is prepared as follows: (1) by proper dilution of a 1 per cent solution of procaine, a solution of 1 cc., containing 0.04 mg., is prepared; (2) 1.0 cc. of this standard is then processed in the same manner as mentioned previously, steps "a" to "e."

g. A Bausch and Lomb, Dubosque type, colorimeter is employed.

The color is light purple, similar to that obtained in the determination of sulfonamides in the blood.

RECOVERY OF PROCAINE ADDED TO BLOOD IN VITRO

The second phase of this investigation was to determine whether procaine, added to oxalated human blood, would be altered in such a manner that accurate determinations could not be done. Known quantities of procaine hydrochloride were added to known quantities of blood so that the concentration was 0.02 to 0.04 mg. per cc. Table 1, which is the average of several determinations, shows that the recovery of procaine hydrochloride was satisfactory.

TABLE 1

Procaine HCl Added to 1.0 cc. Blood	Procaine HCl Determined by This Method
0.020 mg.	0.0206 mg.
0.030 mg.	0.0294 mg.
0.040 mg.	0.0388 mg.

STABILITY OF PROCAINE IN OXALATED BLOOD

Since the recovery of procaine hydrochloride immediately following its addition to blood *in vitro* was satisfactory, determinations of procaine levels were made in other specimens of oxalated blood to which known amounts of procaine had been added. Determinations were made immediately, after one hour, and after twenty-four hours' storage in the ice box (4 to 6 C.) Table 2, which is the average of several determinations, shows that procaine added *in vitro* was stable on standing in the refrigerator, and that there was no apparent loss.

TABLE 2

Procaine HCL Added per cc. of Oxalated Blood	Procaine Recovered (Determination) Time		
	Immediately	1 Hour	24 Hours
0.020 mg.	0.0204 mg.	0.019 mg.	0.019 mg.
0.040 mg.	0.0384 mg.	0.038 mg.	0.037 mg.
0.080 mg.	0.078 mg.	0.079 mg.	0.078 mg.

RECOVERY OF PROCAINE IN THE BLOOD OF RABBITS

Koster (14) has shown the presence in blood, serum and plasma of an enzyme, procaine esterase, which will hydrolyze procaine into para-amino-benzoic acid and diethyl-amino-ethanol. Since the color reaction of the test described is due to the para-amino-benzoic acid of the procaine molecule, the color produced will be proportionate to the concentration of procaine. Although Allen and Livingston (15) concluded that it was not possible to determine by any technic the amount of procaine or para-amino-benzoic acid or sulfanilamide, it is believed that in the control animals the only substance that would be found would be the para-amino-benzoic acid portion of the procaine molecule. The rabbit was chosen because, according to Koster (14), the esterase factor in the rabbit closely approximated the esterase factor of man. A 1 per cent U.S.P. solution of procaine hydrochloride, in a dose of 20 mg. per kilogram of body weight, was injected into the marginal ear vein of rabbits within five to ten seconds. The determinations of procaine levels in the blood stream were made from blood obtained from the same vein as that used for injection. This was done so as not to change the circulating amount of procaine as would occur if other areas of the body were used. Fine (16) et al. have shown that at the site of trauma there is marked capillary permeability. Further trauma to the control animals was not done so that none of the circulating procaine would permeate into the tissues.

Table 3 is an example of the results in rabbits. (Determinations in 2 human beings are added for comparison.)

DISCUSSION

Eggleston and Hatcher (9) and Shumacker (10, 11) demonstrated that the safety of procaine hydrochloride administered intravenously is directly proportional to the decrease of the rate of the injection, the slower the injection the safer. Table 3 demonstrates the conclusion of these authors that procaine will disappear from the blood stream within twenty minutes. This rate of disappearance is so rapid that any determinations to be made will require that the blood specimen be taken either during the injection or no later than twenty minutes after the completion of the injection. The dosage of 20 mg. per kilogram of body weight was selected after trial and error; 40 mg. per kilogram of body

TABLE 3

Subject	Weight, Kg.	Est. Vol. Circ. Blood, cc.	Total Procaine HCl, mg.	Est. Mg. Procaine, per cc.	Time in Minutes after Injection						
					5	8	10	13	15	18	20
Rabbit 1	1.775	110	35.5	0.3227			0.0032				0.0037
Rabbit 2	1.700	105	34.0	0.3238	0.0136	0.0083	0.0074	0.0056		0.0039	
Rabbit 3	1.865	115	37.3	0.3243			0.005		0.0027	0.0021	trace
Rabbit 4	1.600	99.2	32.0	0.3225					0.0100	0.0021	trace
Rabbit 5	1.920	125	38.4	0.3228			0.0069				trace
Rabbit 6	1.650	107.2	33.0	0.3247					0.0030		
Rabbit 7	1.700	110	35.5	0.3227							trace
Rabbit 8	1.800	117	36.0	0.3250					0.0047	0.0047	trace
Rabbit 9	1.825	118.6	36.5	0.3249							trace
Rabbit 10	1.690	109.8	33.8	0.3246			0.0092				
Male (M)	50	3600	200	0.055			0.0044				0.0010
Male (S)	82	5800	500	0.086			faint				
(Given in 25 minutes)				or 0.0011			trace				

Specimens taken 30 minutes after injection contained too little procaine for determination.

weight produced instantaneous death of the animal, and dosages below 20 mg. per kilogram in rabbits gave readings that were too faint to be determined.

On the basis of the above experiment, it was thought that the amount of procaine hydrochloride to be injected into an individual should be that amount which could safely be excreted within twenty minutes. From clinical experience, utilizing a 0.1 per cent solution of procaine hydrochloride in isotonic saline solution, the following dosage was found to give the optimal benefits with the least toxic reaction. This we have called the procaine unit.

$$\frac{\text{4 mg./kilogram body weight}}{\text{in 20 minutes}} = \text{1 Procaine Unit}$$

Utilizing the 0.1 per cent solution, then 1 cc. of solution will contain 1 mg. of procaine hydrochloride.

SUMMARY

Procaine hydrochloride in blood may be determined by the method of Bratton and Marshall. The method can be used in determining blood levels during treatment.

Procaine hydrochloride in blood is stable for at least twenty-four hours when stored in the refrigerator.

Procaine hydrochloride disappears from the blood stream of rabbits and human beings within thirty minutes after intravenous injection.

The authors wish to acknowledge the cooperation and technical assistance of Dr. J. T. Myers and Mr. J. A. Ackerman, of New York, in developing this analytical method.

REFERENCES

1. Allen, F. M.: Intravenous Obstetrical Anesthesia, Am. J. Surg. **70**: 283–290 (Dec.) 1945.
2. Allen, F. M.; Crossman, L. W., and Lyons, L. V.: Intravenous Procaine Analgesia, Anesth. & Analg. **25**: 1–9 (Jan.–Feb.) 1946.
3. Burstein, C.: Treatment of Acute Arrhythmias During Anesthesia by Intravenous Procaine, Anesthesiology **7**: 113–121 (Mar.) 1946.
4. Gordon, R. A.: Intravenous Novocaine for Analgesia in Burns, Canadian M. A. J. **49**: 478–481 (Dec.) 1943.
5. McLachlin, J. A.: Intravenous Use of Novocaine as Substitute for Morphine in Postoperative Care, Canadian M. A. J. **52**: 383–386 (Apr.) 1945.
6. State, D., and Wangensteen, O. H.: Procaine Intravenously in Treatment of Delayed Serum Sickness, J. A. M. A. **130**: 990–995 (Apr. 13) 1946.
7. Applebaum, E.; Abraham, A., and Sinton, W.: A Case of Serum Sickness Treated with Procaine Intravenously, J. A. M. A. **131**: 1274–1275 (Aug. 17) 1946.
8. MacCormac, H.; Sandifer, P. H., and Jelliffe, A. M.: The Itchy Patient, Brit. Med. J. **2**: 48, 1946.
9. Eggleston, C., and Hatcher, R. A.: Pharmacology of Local Anesthetics, J. Pharmacol. & Exper. Therap. **13**: 433, 1919.
10. Shumacker, H. B., Jr.: Reactions to Local Anesthetic Agents, Survey **10**: 119–133 (July) 1941.
11. Shumacker, H. B., Jr.: Some Observations on the Rate of Absorption from Various Body Tissues, Surgery **12**: 81–87 (July) 1942.
12. Bandelin, F. J., and Kemp, C. R.: Colorimetric Determination of Local Anesthetic Compounds, Indust. & Engin. Chem. **18**: 470, 1946.
13. Bratton, A. C., and Marshall, E. K.: A New Coupling Element for Sulfanilamide Determinations, J. Biol. Chem. **128**: 537, 1939.
14. Goldberg, A.; Koster, H., and Warshaw, R.: Fate of Procaine in the Human Body after Subarachnoid Injection, Arch. Surg. **46**: 49–58 (Jan.) 1943.
15. Allen, J. G., and Livingstone, H.: The Absorption, Conjugation, Diffusion and Excretion of Procaine in the Rabbit, Anesth. & Analg. **21**: 285–289 (Sept.–Oct.) 1942.
16. Fine, J., and Seligman, A. M.: A Study of the Problem of the Lost Plasma in Hemorrhagic Tourniquet and Burn Shock by the Use of Radioactive Iodo Plasma Protein, J. Clin. Invest. **23**: 720–730 (Sept.) 1944.
17. Smith, P. K.: The Use of Para-Aminobenzoic Acid in Endemic (Murine) Typhus, J.A.M.A. **131**: 1114–1117 (Aug. 3) 1946.

The following are the officers for the Kansas City Society of Anesthesiology for the current year:

President: Dr. L. Lafe Bresette (reelected).
President Elect: Dr. C. R. McCubbin.
Vice President: Dr. Helen Kingsbury (reelected).
Secretary: Dr. Paul H. Lorhan (reelected).
Treasurer: Dr. Louis Porter.

The following officers of the Section of Anesthesia of the Connecticut State Medical Society were elected for the coming year:

Stevens J. Martin, M.D., Hartford, Conn.—President of the State Society of Anesthesia and Chairman of the Section of Anesthesia.

Arthur Adams, M.D., Torrington, Conn.—Secretary-Treasurer.

Dr. Charles Barber, M.D., Hartford, Conn., was appointed by the President as Chairman of the Program Committee.

USE OF A NEW CURARIZING AGENT, DIHYDRO-BETA-ERYTHROIDINE, FOR THE PRODUCTION OF MUSCULAR RELAXATION DURING ANESTHESIA AND SURGERY *

ROBERT D. DRIPPS, M.D., AND WARREN F. SERGENT, M.D.

Philadelphia, Pa.

Received for publication November 9, 1946

THIS report concerns the intravenous administration of a relatively new curarizing agent, dihydro-beta-erythroidine,† to 215 patients receiving general anesthesia. These preliminary studies indicate that muscular relaxation satisfactory for all types of surgery can be provided with this substance, but that because of the production of hypotension the drug may have definite disadvantages in clinical practice.

For several reasons it seemed worthwhile to study dihydro-beta-erythroidine in clinical anesthesia, where its ability to decrease or abolish muscle tone through an action at the nerve-muscle junction resembled that of curare. The drug is a crystalline product and can be weighed accurately. Thus, a solution can be prepared in which the number of milligrams per cubic centimeter is known. This is preferable to solutions in which potency is determined in units according to bio-assay. Of interest, also, is the finding that dihydro-beta-erythroidine does not appear to possess the histamine-like properties attributed to curare and its derivatives. Comroe and Dripps (1) found that the intra-arterial or intracutaneous injection of dihydro-beta-erythroidine in man did not produce histamine-like wheals, although curare (intocostrin) and d-tubocurarine chloride were followed by such a reaction. Landmesser (2) noted bronchoconstriction and hypotension in spinal dogs when curare and its derivatives were injected intravenously but in similar experiments bronchoconstriction did not occur and the fall in blood pressure was less after administration of dihydro-beta-erythroidine.

HISTORY

The natural source of dihydro-beta-erythroidine is *Erythrina* L., a genus of trees and shrubs with showy flowers of various shades of red which is widely distributed over the tropics and subtropics of the entire

* From the Department of Anesthesia, Hospital of the University of Pennsylvania and the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine, Philadelphia.

† The drug was supplied through the courtesy of Merck and Company, Rahway, N. J.

globe. In 1877 extracts of the bean-like seeds of these plants were reported to paralyze animals.

Sporadic studies on the effects of the *Erythrina* seeds were reported in the literature until 1935 when Ramirez and Rivero (3) reaffirmed the curarizing action already noted. In 1937 Folkers and Major (4) isolated an alkaloid, erythroidine, from *Erythrina Americana* Mill. This consisted of a mixture of at least two isomeric alkaloids, named alpha and beta-erythroidine. Since the beta-form was more readily obtainable in the pure state, chemical and clinical investigations centered on this substance. Beta-erythroidine is a tertiary ammonium base, forming crystalline acid salts which are freely soluble in water. This drug possessed definite curarizing properties. It was first used in clinical medicine in 1939 by Burman (5) who employed it as a substitute for curare in the treatment of spastic dystonia. It was next used by Rosen and coworkers (6) to prevent fractures secondary to metrazol convulsion therapy.

A disadvantage of beta-erythroidine was the brevity of its action. Following intravenous administration, block of conduction at the myoneural junction disappeared within five to ten minutes (7). In 1944 Unna and colleagues (8) reported pharmacologic studies of a halogenated derivative of beta-erythroidine, dihydro-beta-erythroidine. This substance was two to ten times more toxic than beta-erythroidine but was six times as potent from the standpoint of curarization. Furthermore, the duration of action of dihydro-beta-erythroidine was considerably longer.

PRESENT STUDY

One hundred and eighty-seven female and 28 male patients were observed in this study. The average age of the group was 43 years, with a range of 12 to 78 years. The average weight of the group was 140 pounds, with a range of 88 to 280 pounds.

No attempt was made to select cases. Patients with coronary artery disease, hypertension, diabetes mellitus, pulmonary tuberculosis, emphysema, intestinal obstruction, liver and renal disease were included. Cyclopropane was the anesthetic agent in 191 instances, ethyl ether (nitrous oxide induction) in 19, sodium pentothal in 3, and nitrous oxide in 1. For administration of the inhalation anesthetics the carbon-dioxide absorption, circle filter, technic was used in all but 6 cases. With the exception of 6 patients the group received morphine sulfate 10 mg. (1/6 grain) and atropine sulfate 0.4 mg. (1/150 grain) hypodermically as preoperative medication. As indicated in table 1, all types of abdominal surgery were included.

The average duration of the surgical procedures was fifty-five minutes, with a range of twenty to two hundred twenty-five minutes.

TABLE 1

TYPE OF OPERATION

	Cases
I. Upper Abdominal Surgery	
Cholecystectomy	14
Common duct exploration	10
Gastric resection	9
Splenectomy	6
Exploratory laparotomy	3
Renal surgery	3
Excision of pancreatic cyst	1
	46
II. Lower Abdominal Surgery	
Gynecologic—supravaginal or total hysterectomy, salpingo-oophorectomy	114
Appendectomy	11
Suprapubic prostatectomy	8
Exploratory laparotomy	6
Herniorrhaphy	5
Colostomy	4
Colon resection	4
	152
III. Miscellaneous	17
Total	215

RESULTS

1. *Effects on Myoneural Junction.*—Dihydro-beta-erythroidine decreased or abolished the conduction of impulses from nerve to skeletal muscle in a curariform fashion. Muscles were affected in the same sequence as with curare and its derivatives, i.e., muscles supplied by the cranial nerves first, extremity, abdominal and thoracic muscles next in that order, and finally the diaphragm. Any extent of muscular flaccidity could be produced by varying the dose of dihydro-beta-erythroidine. In the conscious individual small doses produced ptosis and diplopia alone, while larger doses were not infrequently followed by respiratory arrest secondary to paralysis of all voluntary muscles.

(a) Abdominal muscular relaxation. Clinical appraisal of the degree of muscular relaxation produced by a particular agent is difficult. What is regarded as a relaxed abdomen by one surgeon may be unsatisfactory to another. As Gillespie (9) has pointed out, "muscular relaxation" may not be judged entirely by the degree of flaccidity. Spasm of the vocal cords or excessive descent of the diaphragm may prove just as annoying to the surgeon as a contracted abdominal wall. It is difficult, therefore, for one clinic to evaluate the utility of a drug as far as the production of adequate surgical working conditions is concerned. We can only report that dihydro-beta-erythroidine seems indistinguishable in this regard from curare. Satisfactory surgical relaxation was recorded in 96 per cent of the cases.

(b) Respiratory muscles. The following degrees of respiratory depression were noted in the 195 cases in which such data were recorded; mild 57 (29 per cent), moderate 73 (38 per cent) and severe 65 (33 per cent). Respiratory depression was characterized as "mild" if the minute volume was only slightly decreased, and as "moderate" if minute volume was decreased to a greater extent and some degree of intercostal muscle paralysis was observed. The category "severe" included those instances in which respiration was maintained primarily by the diaphragm and accessory muscles, or in which all respiratory activity ceased and manual pressure on the breathing bag was required. It is evident that, as with curare, if this drug is to be used the anesthetist must be prepared to deal effectively with severe respiratory depression. The decrease in respiratory minute volume was accomplished almost entirely by a diminution in depth per breath. Respiratory rate remained relatively unchanged, or increased. Quantitative aspects of the respiratory action of dihydro-beta-erythroidine are being studied at the present time.

As might be expected, dihydro-beta-erythroidine exerted a paralytic effect on striated laryngeal muscles. Since endotracheal intubation was used in only 8 of the 46 instances of upper abdominal operations, there was ample opportunity for the development of reflex adduction of the vocal cords. Anesthesia was maintained in first or upper second plane in the majority of cases and afferent impulses from the operative site not infrequently resulted in partial respiratory obstruction and "crowing." The intravenous administration of additional doses of dihydro-beta-erythroidine decreased or abolished this laryngeal spasm. Direct inspection of the larynx revealed partial or complete paralysis of both adductor and abductor muscles at this time.

(c) Another action of this drug which may be related to paralysis of muscle tone was pupillary dilatation which occurred in about one-half of the cases. Since the iris muscle of birds has been reported to resemble striated muscle to a greater degree than most smooth muscle, the possibility of this pupillary response being related to a myoneural block action is being investigated. The phenomenon did not seem to be related to anoxemia.

The duration of action of a single dose of dihydro-beta-erythroidine varied as far as these muscular effects were concerned. As a rule pupillary dilatation was transient, beginning to regress within three to five minutes. Maximal respiratory depression was noted within three to five minutes of the intravenous injection of the drug. Reversal began within another three to five minutes. Abdominal relaxation of a degree adequate for surgical intervention persisted for twenty to thirty minutes.

2. *Effects on the Circulation.*—The major complication of the intravenous administration of dihydro-beta-erythroidine was the hypoten-

sion which occurred in 174 (86 per cent) of the 202 patients on whom circulatory data were available (table 2.)

The greater degree of hypotension noted after the initial injection was due to the fact that this was usually the largest dose, and the amount of blood pressure decrease was related in part at least to the amount of drug administered. It is interesting to observe that subsequent doses had the same tendency to reduce blood pressure as did previous injections. Tachyphylaxis (development of drug resistance), therefore, was not observed, nor was there any increased response to successive doses. We also gained the impression that the degree of hypotension produced was related to the level of anesthesia. The more profound the narcosis the greater appeared to be the circulatory depression. This is being studied quantitatively at the present time.

TABLE 2

Average Decrease in Blood Pressure Following the Intravenous Administration of Dihydro-beta-erythroidine

	Systolic, mm. of mercury	Diastolic, mm. of mercury	No. of Cases
1st Injection	24	16	174
2nd Injection	15	9	151
3rd Injection	15	8	78
4th Injection	15	11	42
5th Injection	13	9	18

The fall in blood pressure as a rule was a transient phenomenon, rarely lasting more than five minutes, although in an occasional patient a lowered blood pressure persisted for ten to fifteen minutes. This was particularly true for individuals anesthetized with ether. In some patients the degree of hypotension was marked. The greatest decrease in pressure was 100 mm. of mercury systolic and 60 mm. of mercury diastolic in a patient whose initial blood pressure was 140 mm. systolic and 80 mm. diastolic. In 8 patients the injection was followed by a greyish cyanosis of the face, although the color of the blood in the operative field appeared normal in most of these individuals.

That the erythrina alkaloids lower blood pressure in intact man and animals has been reported by others (8, 10, 11). The cause of this response has not been elucidated. Landmesser (2) has observed that dihydro-beta-erythroidine has little tendency to lower blood pressure in spinal dogs. The presence of an intact medulla or of higher centers in the central nervous system, therefore, appears essential. In a few preliminary studies on the mechanism of the depressor response we have noted no change in stroke volume or cardiac output per minute. Harvey and Masland (7), however, have recorded a slight decrease in cardiac output following administration of beta-erythroidine in unanesthetized man. It seems likely that the reaction is related

primarily to depression of the medullary vasoconstrictor center or to paralysis of sympathetic ganglia with diminution of arteriolar tone. If this were the only cause, however, one might expect a greater decrease in diastolic pressure than we have recorded. Perhaps observations made by auscultation under clinical conditions were misleading, and the diastolic pressures were actually lower than indicated in table 2.

This hypotensive reaction to dihydro-beta erythroidine proved to be the major objection to clinical use of the drug despite the relatively brief nature of the response. Curare and its derivatives do not cause a similar depression of blood pressure. Attempts to minimize the reaction by decreasing the rate of injection or by administering the drug in divided doses have so far proven unsuccessful.

The average changes in pulse rate for the group were not significant, but marked variations were noted in individual responses (table 3).

TABLE 3

CHANGE IN PULSE RATE PER MINUTE FOLLOWING THE INTRAVENOUS ADMINISTRATION OF DIHYDRO-BETA-ERYTHROIDINE

	Average Change	Range	Total Cases
1st Injection	+2	−40 to +40	158
2nd Injection	+1	−38 to +40	141
3rd Injection	+1	−25 to +22	79
4th Injection	+2	−10 to +15	20
5th Injection	−2	−14 to +12	8

Unna and coworkers (8) reported that the erythrina alkaloids produce a marked bradycardia in some anesthetized dogs. This cardiac slowing occurred despite block of the vagus nerves by atropine or nerve section. We have confirmed the occurrence of bradycardia following dihydro-beta-erythroidine after large (2.5 mg.) doses of atropine in man. In 2 of the 4 individuals given this amount of atropine intravenously, the pulse rate fell from 144 to 100, and from 126 to 100, respectively, after the administration of dihydro-beta-erythroidine. In the other 2 subjects the pulse rate remained essentially unchanged. This bradycardia could be due to paralysis of sympathetic ganglia.

3. *Effects on the Central Nervous System.*—Earlier pharmacologic teaching gave the impression that the only action of curare, its derivatives and substitutes involved block of conduction at the nerve-muscle junction. The circulatory depressant action described suggests the possibility of direct depression of the medullary vasomotor center. There is also other evidence in man and animals which indicates that curare and the erythrina alkaloids depress the central nervous system.

Curare, d-tubocurarine, and dihydro-beta-erythroidine have been reported to inhibit and finally suppress electrical activity of the frog

brain (12). Curare and dihydro-beta-erythroidine decrease the heat production of the brain (13). This effect of these drugs is not reversed by prostigmin. Indeed, prostigmin itself tends to suppress the electrical activity of the brain. Burman (14) accidentally swallowed one of the erythrina alkaloids and observed in himself a profound hypnotic effect. In clinical practice Whitacre and Fisher (15) have reported loss of consciousness following the administration of large doses of curare. Harvey and Masland (7) have made the statement that "erythroidine frequently produces unquestionable mental changes" in conscious individuals, characterized by drowsiness, confusion, even irrationality. These authors attempted to demonstrate a cerebral action by studying changes in the electroencephalogram during the administration of curare and erythroidine. In several instances during the recording, mild mental confusion occurred, but in no case was it accompanied by any distinct change in the electroencephalogram. Roseman and coworkers (11) administered dihydro-beta-erythroidine to anesthetized cats and recorded changes in the electrical activity of the cerebral cortex. There was no appreciable change in frequency and only a slight, transient diminution in amplitude of action potentials following administration of the drug.

There are, therefore, conflicting reports, but enough data are available to focus attention on the action of curarizing drugs on the central nervous system. Whether the effects noted are the result of a direct action on cells of the cerebral cortex or are secondary to a block at synapses remains to be determined.

The possibility of this central nervous system action having clinical significance must be considered (16). In several instances we have gained the impression that the patient has remained depressed for longer than the degree of general anesthesia would have suggested. We have no definite data on this point, but believe further investigation is indicated employing neuro-physiologic technics.

4. *Action with Various Anesthetic Agents.*—Although most of the patients in this series were anesthetized with cyclopropane, 19 received nitrous-oxide induction followed by ethyl ether. In these latter patients the degree of muscular relaxation and respiratory depression was greater at comparable levels of anesthesia and with comparable doses of dihydro-beta-erythroidine than during cyclopropane anesthesia. This was to be expected from the known curariform action of ethyl ether (18, 19, 20). Circulatory depression also was more marked when dihydro-beta-erythroidine was administered to patients receiving ether. In 3 individuals a drop of blood pressure level to zero was recorded. Fortunately, a prompt return of blood pressure to normal occurred in each case.

In the 3 individuals given sodium pentothal, a greater degree of nerve-muscle block was also noted. From the technical standpoint, Cole (17) reported the formation of a precipitate when pentothal is

added to a curare solution. A similar reaction occurs when pentothal is added to dihydro-beta erythroidine. Both reactions are due to the fact that any alkali (such as sodium pentothal) will precipitate an alkaloidal acid salt. The alkaloidal base is precipitated.

Dihydro-beta-erythroidine did not prevent the occurrence of cardiac arrhythmias under cyclopropane anesthesia.

5. *Postoperative Course.*—An attempt was made to maintain most patients in the upper planes of surgical anesthesia. Because of this minimal narcosis, recovery from anesthesia was more rapid than in the usual case of intra-abdominal surgery. Excitation during the immediate postoperative period was therefore not uncommon.

Although a comparative study has not been made of patients anesthetized by other methods, certain data have been recorded for the group receiving dihydro-beta-erythroidine. Data obtained postoperatively relating to the gastrointestinal tract were recorded for 165 patients as follows:

	No. of Cases
Vomiting 1–2×	35
Vomiting 3–4×	34
Vomiting >4×	15
	84 (51%)
Nausea only	27 (16%)
No nausea or vomiting	54 (33%)

Urinary retention of some degree occurred in 43 (29%) of 151 patients on whom data are available:

No. of Catheterizations	No. of Cases
1–2×	28
3–4×	8
>4×	7

One instance of postoperative bronchopneumonia was observed in the 215 patients; there were no cases of atelectasis.

Five patients in the series died. The first was an emaciated 37-year-old woman who died on the third day after her fourth operation for intestinal ulceration and infection of two years' duration and of unknown etiology. The second was a 53-year-old man who failed to survive exploratory operation which revealed an extensive mesenteric thrombosis. The third was a 63-year-old woman with peritoneal carcinomatosis, ovarian in origin. She died two days after an exploratory laparotomy. The fourth was a 71-year-old man with a six day history of left-sided obstruction of the large bowel. Before operation he was cold and clammy, with a subnormal body temperature. Although only a sigmoidostomy was performed and the patient left the operating room apparently unharmed by the procedure, he failed to rally and died of uremia on the seventh postoperative day. Since there was no circulatory depression in this individual following administration

of the dihydro-beta-erythroidine, we do not believe that the drug can be implicated; indeed, it is unlikely that its administration was related in any way to the death of these 4 patients.

The circulatory depression caused by this drug may have been a factor in the fifth fatality. This was a 74-year-old man, 5½ feet tall, weighing 190 pounds. His preoperative blood pressure was 150 mm. systolic and 90 mm. diastolic, and pulse rate 120. Suprapubic prostatectomy was performed under cyclopropane anesthesia. The patient was in a moderate Trendelenburg position. Ten minutes after the start of the operation, 150 mg. of the dihydro-beta-erythroidine was administered. The patient was in the second plane of the third stage of surgical anesthesia at this time. The injection produced marked respiratory depression which necessitated manual pressure on the breathing bag. A drop in blood pressure to 70 mm. systolic and 40 mm. diastolic occurred within one minute. Successive minute to minute readings thereafter were: 90/50, 106/60, 112/70, 112/80, 120/80, 126/90, 140/100, 150/100. Twenty minutes before the conclusion of the operation, with the blood pressure 150 mm. systolic and 100 mm. diastolic, the patient was returned to the horizontal position. Blood pressure began to fall slowly and at the end of fifteen minutes had reached 96 mm. systolic and 70 mm. diastolic. Citrated blood was administered intravenously. The operation was completed in fifty minutes. After the anesthesia mask was removed the blood pressure reading fell to 80 mm. systolic and 56 mm. diastolic. The patient reacted promptly, was returned to his room and conversed intelligently with his nurse for one hour, when he suddenly gasped and fell over dead. Necropsy revealed coronary thrombosis.

This patient was subjected to two episodes of hypotension, either one of which or both could have set the stage for clot formation in the coronary arteries. In defense of the drug it might be stated that 150 mg. is an excessive dose, particularly for such an elderly patient, in whom the depth of narcosis was greater than necessary.

Dosage

The initial dose of dihydro-beta-erythroidine varied considerably in this series. It ranged from 75 to 225 mg. The average total dose was 240 mg., with a range of 75 to 800 mg. The initial dose which we recommend on the basis of this study is 50 to 75 mg. if ethyl ether anesthesia is employed, and 75 to 100 mg. if the anesthetic agent is cyclopropane. The reason for the difference in doses is related to the curariform action of ether.

Prostigmin is the pharmacologic antidote to dihydro-beta erythroidine as far as the myoneural junction is concerned. At no time was it necessary to employ this drug, but it was administered on several occasions to confirm previous observations of its effectiveness.

COMMENT

Dihydro-beta-erythroidine has been found by others to possess a typical curare-like action on the nervous system. We have, therefore, used this drug in clinical anesthesia as a substitute for curare. Our experience indicates that any desired extent or degree of weakness or paralysis of striated muscle can be produced by varying the dose of this erythrina alkaloid. As a consequence, satisfactory relaxation for abdominal operations, for release of mandibular muscular spasm or laryngeal spasm, and for diminution or abolition of other types of voluntary muscular spasm can be produced promptly by the intravenous administration of this substance. The drug is effective as far as the anesthetist and surgeon are concerned whether the anesthetic agent be cyclopropane, ethyl ether, sodium pentothal or nitrous oxide. The paralytic action is significantly greater when it is used in combination with ether.

The usefulness of a curarizing drug in the production of muscular relaxation during anesthesia and surgery cannot be questioned. The ideal substance would be one which blocked conduction peripherally at the nerve-muscle junction and had no other action. It appears that neither curare and its derivatives nor the erythrina alkaloids meet this requirement. The former group of drugs depress the central nervous system and cause the liberation of histamine from body tissues in sufficient amounts to produce bronchoconstriction, which may be marked. The latter also have a central nervous system action. Either as part of this central effect or as the result of some other mechanism, there is a well-defined decrease in the blood pressure level following the intravenous administration of the erythrina series to anesthetized man. It seems likely that this hypotensive action of dihydro-beta-erythroidine would be of much more concern to the clinician than is the bronchoconstriction and decrease in blood pressure level which may be caused by curare or d-tubocurarine.

At the present writing no successful technic has been discovered which can prevent this lowering of blood pressure when dihydro-beta-erythroidine is administered intravenously. It is possible that a further reduction in the dose or in the rate of injection might be helpful. The use of pressor drugs has not been attempted.

Since the erythrina group of drugs are effective when taken orally, and since they appear of value in the treatment of certain neurologic muscular disorders, further investigation of these substances is indicated. Their ultimate place in clinical anesthesia, however, remains uncertain.

CONCLUSION

A relatively new curarizing agent, dihydro-beta-erythroidine, has been administered intravenously to 215 patients for the production of

muscular relaxation during operation. The action of this substance on the nerve-muscle junction was indistinguishable from that of curare.

The major complication following dihydro-beta-erythroidine was the hypotension which occurred in 86 per cent of the patients. This reaction may prevent the drug from being useful in clinical anesthesia. Since the alkaloid is effective when taken by mouth and since it has proved of value in the treatment of certain diseases of the central nervous system, further investigation of its action is indicated.

REFERENCES

1. Comroe, J. H., Jr., and Dripps, R. D.: The Histamine-like Action of Curare and Tubocurarine Injected Intracutaneously and Intra-arterially in Man, Anesthesiology 7: 260–262 (May) 1946.
2. Landmesser, C. M.: A Study of the Bronchoconstrictor and Hypertensive Actions of Curarizing Drugs (To be published).
3. Ramirez, E., and Rivero, N. D.: Contribucion al Estudio de La Accion Farmacodynamica de La Erythrina Americana, Anales Inst. Biol. (Mex.) 6: 301–310, 1935.
4. Folkers, K., and Major, R. T.: Isolation of Erythroidine, an Alkaloid of Curare Action, from Erythrina Americana Mill, J. Am. Chem. Soc. 59: 1850, 1937.
5. Burman, M. S.: Therapeutic Use of Curare and Erythroidine Hydrochloride for Spastic and Dystonic States, Arch. Neur. & Psych. 41: 307 (Feb.) 1939.
6. Rosen, S. R.; Cameron, D. E., and Ziegler, J. B.: Prevention of Metrazol Fractures by Beta-Erythroidin Hydrochloride, Psychiat. Quart. 14: 477–480 (July) 1940.
7. Harvey, A. M., and Masland, R. L.: Actions of Curarizing Preparations in the Human, J. Pharmacol. & Exper. Therap. 73: 304–311 (Nov.) 1941.
8. Unna, K.; Kniazuk, M., and Greslin, J. G.: Pharmacologic Action of Erythrina Alkaloids. 1. Beta-erythroidine and Substances Derived from It, J. Pharmacol. & Exper. Therap. 80: 39–52 (Jan.) 1944.
9. Gillespie, N. A.: Relaxation: A Meditative Essay, Anesthesiology 1: 292–299 (Nov.) 1940.
10. Lehman, A. J.; Chase, H. F., and Yonkman, F. F.: Some Quantitative Comparisons of Quinine Ethochloride Dihydrate, Quinine Methochloride Dihydrate, Beta-Erythroidine Hydrochloride and Dihydro-beta-Erythroidine Hydrobromide, J. Pharmacol. & Exper. Therap. 75: 270–276 (July) 1942.
11. Roseman, E.; Goodwin, C. W., and McCulloch, W. S.: Rapid Changes in Cerebral Oxygen Tension Induced by Altering the Oxygenation and Circulation of the Blood, J. Neurophysiol. 9: 33–40 (Jan.) 1946.
12. Pick, E. P., and Unna, K.: The Effect of Curare and Curare-like Substances on the Central Nervous System, J. Pharmacol. and Exper. Therap. 83: 59–70 (Jan.) 1945.
13. Feitelber, S., and Pick, E. P.: Action of Curare on the Brain of the Frog, Proc. Soc. Exper. Biol. & Med. 49: 654–656 (Apr.) 1942.
14. Burman, M. S.: Clinical Experiences with Some Curare Preparations and Curare Substitutes, J. Pharmacol. & Exper. Therap. 69: 143–148 (June) 1940.
15. Whitacre, R. J., and Fisher, A. J.: Clinical Observations on the Use of Curare in Anesthesia, Anesthesiology 5: 124–130 (Mar.) 1945.
16. Griffith, H. R.: Physiological and Clinical Action of Curare, Anesth. & Analg. 25: 45–51 (Mar.) 1946.
17. Cole, F.: The Use of Curare in Anesthesia; A Review of 100 Cases, Anesthesiology 6: 48–56 (Jan.) 1945.
18. Auer, J., and Meltzer, S. J.: The Effect of Ether Inhalation Upon the Skeletal Motor Mechanism, J. Pharmacol. & Exper. Therap. 5: 521–522, 1914.
19. Gross, E. G., and Cullen, S. C.: The Effects of Anesthetic Agents on Muscular Contraction, J. Pharmacol. & Exper. Therap. 78: 358–365 (Aug.) 1943.
20. Comroe, J. H., Jr., and Dripps, R. D.: The Action of Anesthetic Agents on Nerve-Muscle Conduction in Man (To be published).

CURARE AND CURARE-LIKE COMPOUNDS: A REVIEW

BENJAMIN H. ROBBINS, M.D., Fellow in Anesthesiology, Mayo Foundation, AND JOHN S. LUNDY, M.D., Section on Anesthesiology, Mayo Clinic

Rochester, Minnesota

Received for publication October 8, 1946

N. B. The label on the Squibb ampule reads, in part, "Each cc. has a potency equivalent to 20 units of Standard Drug." And, to quote from the *Journal of the American Medical Association*, October 13, 1945, page 517: "The physiologic activity of intocostrin is determined on rabbits: the provisional unit is equivalent to the potency of 0.15 mg. of d-tubocurarine chloride." Therefore, each cubic centimeter of intocostrin has a potency equivalent to 3 mg. of d-tubocurarine chloride ($0.15 \times 20 = 3.0$). This information is important in the future use of other brands of curare, the label on which may read in milligrams rather than in Squibb units.

In the present review, doses have been given exactly as the original authors gave them in their papers. In some instances, however, it appears that an author spoke of "milligrams of curare" when he actually meant "units of intocostrin."

IT has seemed to us that the increased interest in curare, from both the experimental and the clinical points of view during the past decade, has made it desirable to collect in a single paper some of the more important steps which led up to present knowledge relating to this most interesting and active substance. Therefore, it is our purpose in this paper to trace the historical development of curare, from its use as an arrow poison by South American Indians down to the isolation of the active agent, d-tubocurarine chloride, a chemically pure crystalline compound, and the use of this substance in man. Likewise, in this review the development of erythroidine and quinine derivatives which have curare-like action will be discussed in relation to curare. The similarity of the effects of erythroidine and quinine derivatives in the laboratory animal and in man also will be set forth.

The word "curare" will be used when the agent was obtained as the crude dried extract from whatever source. "Curarine" will be employed to denote a relatively pure alkaloid from *Strychnos toxifera*. "Intocostrin" identifies a biologically standardized form of curare. "D-tubocurarine chloride" refers to the crystalline, chemically pure, active material obtained from the plant, pareira, or *Chondrodendron tomentosum*.

CURARE

Sources of Curare.—The main geographic sources of crude curare are the northern and northwestern basins of the Amazon River, the

upper part of the Orinoco basin, British Guiana and eastern Ecuador (1, 2).

The botanic sources of curare are variable. Considerable confusion characterized the earlier literature because of lack of exact data in the correlation of crude curare with definite botanic sources. Then, too, the natives who supplied the curare mixed material obtained from many plants and herbs in their stew. Sollmann (3) stated that curare is obtained from various species of *Strychnos* such as (*S. toxifera* and *S. castelnaei*). The twelfth revision of the *Pharmacopoeia of the United States* (4) lists three species of *Strychnos* as sources. Folkers (5) reported that at least five species of *Strychnos* used by South American Indians in the preparation of curare contained quaternary ammonium alkaloids that have paralytic action. Gill (1, 6), McIntyre and King (7), Bennett (8), Wintersteiner and Dutcher (9) stated that curare is obtainable from *Chondrodendron tomentosum.*

King (10), who first isolated and determined the chemical formula of d-tubocurarine chloride from tubocurare of an unknown plant source in 1935, pointed to members of the genus *Chondrodendron* as probable sources of the active ingredients of crude curare.

Gill (1, 11) collected and made curare in the field from vines identified as *Chondrodendron tomentosum;* this work represented the first time that the exact source of a form of curare was recorded. This "authenticated" type of curare formed the basis of McIntyre's studies as well as the source of material from which Wintersteiner and Dutcher in 1943 prepared their crystalline d-tubocurarine chloride.

Chemical Aspects.—The early samples of curare were prepared by the making of a water extract of leaves, bark, stems and roots of many plants. The liquid was strained off and evaporated to a thick syrup or to dryness, and was brought out from the site of preparation in one of three types of containers: bamboo tubes, gourds or earthenware pots. The name of the container used was given to its contents; hence such appellations as tubocurare, calabash curare or pot curare.

Boehm (12) reported the isolation of different alkaloids from the three different types of crude curare; King (10) later made the same observation.

For many years it was thought that the curare exported in the three aforementioned types of containers had been obtained and prepared from different types of curare-containing plants, but Gill (1) recently discounted this idea, saying that regardless of the plants from which a given batch of curare had been prepared, the batch was simply placed in the most accessible container.

The preparation of "intocostrin" as described by the makers in the article of acceptance by the Council on Pharmacy and Chemistry of the American Medical Association (13) is given below:

"Intocostrin prepared from Chond[r]odendron tomentosum extract is made by first extracting with alcohol a desiccated curare obtained from a heavy syrup

of the bark and stems of Chrond[r]odendron tomentosum. The alcoholic extract is evaporated to dryness; a sterile filtered solution having a pH of 4.6 – 4.8 is made and adjusted to a standard potency of 20 units per cubic centimeter. The final solution contains sodium chloride 0.45 per cent and trichlorobutanol 0.5 per cent; sterilized by filtration and its pH again adjusted to 4.6 – 4.8.

"In the preparation of intocostrin from pure d-tubocurarine chloride crystals, the crystals are obtained from the desiccated curare or from the crude syrup. . . .

"The physiologic activity of intocostrin is determined on rabbits: the provisional unit is equivalent to the potency of 0.15 mg. of d-tubocurarine chloride."

Numerous chemical studies have been made on various samples of curare of unknown sources, and the lack of homogeneity and of adequacy of the size of the samples may account in part for the different results published in the literature.

Boehm (12) obtained curarine ($C_{19}H_{26}N_2O$) from gourd curare, protocurarine ($C_{19}H_{25}NO_2$) from pot curare and tubocurarine ($C_{19}H_{21}NO_4$) from tubocurare. In addition to these quaternary ammonium bases, he obtained some tertiary ammonium bases. Later, King (10) obtained crystalline d-tubocurarine chloride ($C_{38}H_{44}O_6N_2Cl_2$) from a sample of tubocurare, and as a result of studies of degradation products, proposed the structure for this substance that appears in figure 1.

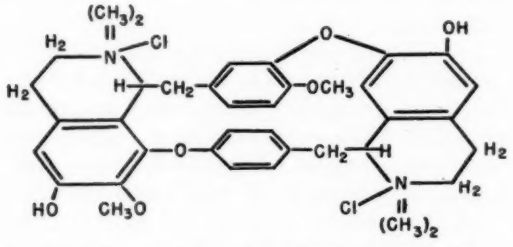


FIG. 1. Representation of the structure of d-tubocurarine chloride as proposed by King (10).

Wintersteiner and Dutcher (9) reported the isolation and chemical characterization of d-tubocurarine chloride from curare known to be prepared from *Chondrodendron tomentosum*. Their empiric formula ($C_{38}H_{44}O_6N_2Cl_2$) is the same as that of King, and their structural formula is the same except for the location of one methoxy group. They stated that their substance is identical to that of King. Wintersteiner and Dutcher prepared what proved to be identical to the dimethylether iodide of d-tubocurarine, and it is interesting to note that this new substance is about nine times as active physiologically as the parent compound.

Wieland, Konz and Sonderhoff (14) have isolated from gourd curare a crystalline compound, toxiferine ($C_{25}H_{27}O_2N_3 \cdot HCl$), which contains no methoxy groups or phenolic hydroxyl radicals. This substance is a very active curarizing agent.

Experimental Studies in the Laboratory and Other Studies.—Brodie (15), as early as 1811, observed that curare poisoned warm-blooded animals by depression of respiration, although the site of action of curare in producing this decrease in respiration was not localized until the studies of Pelouze and Bernard (16) and Bernard (17) showed the action to be peripheral. At about the same time, Kölliker (18) published his studies on the site of action of curare.

During the intervening years a great number of studies have been reported on the action of curare on various animals and on patients suffering from various diseases. In most of the earlier experimental studies the curare employed was very impure; because of this impurity determinations of the secondary effects, other than the effect on the skeletal nerve-muscle system, are not consistent from curare to curare or from investigator to investigator.

The studies of Boehm (12), from both the chemical and pharmacologic points of view, extending from 1894 to 1920 with his extensive review, cover very well the earlier observations on curare.

Skeletal Nerve-Muscle Studies.—Studies on the effect of curare or its derivatives on the nerve-muscle system vary from those of Bernard (17), who used curare in the whole frog, to those of Steiman (19), who studied the effect of curare on an efferent nerve fiber to a single muscle fiber. Bernard found that when curare was injected into the lymph sac of a frog, the muscle (gastrocnemius) did not contract when the nerve to the muscle was stimulated, but that direct stimulation of the muscle produced a contraction. Steiman, using a nerve-single muscle fiber preparation, found that the addition of curare to the bath soon caused a cessation of contraction on stimulation of the nerve, but that direct stimulation of the muscle fiber resulted in contraction.

The mechanism by which curare blocks the transmission of nerve impulses to the muscle fiber is thought to be due to an increase in the stimulus threshold of the muscle to acetylcholine.

Brinkman and Ruiter (20) perfused the indirectly stimulated muscles of the hind leg of a frog and obtained a substance in the perfusate that was similar in action to acetylcholine. The perfusate obtained on nerve stimulation after complete curarization likewise contained an acetylcholine-like substance.

Dale, Feldberg and Vogt (21) showed that the stimulation of pure motor nerve fibers to voluntary muscles in the dog and cat causes a release of acetylcholine in the venous perfusion fluid. Likewise, they have shown that this acetylcholine is released on stimulation of the nerve after complete curarization by curarine, so that it appears that curarine does not produce its effect by preventing the formation and liberation of acetylcholine, which is thought at present to be the chemical mediator of the transmission of impulses from the nerves to the skeletal muscle.

Brown, Dale and Feldberg (22) compared the effects of the close

intra-arterial injection of minute amounts of acetylcholine to those produced by maximal nerve stimulation in the cat. They found that the contraction produced by acetylcholine was very similar in speed and amplitude to that produced by nerve stimulation. They found also that curarization produced by the intravenous injection of 0.7 mg. of curarine per kilogram of body weight decreased markedly the contraction on nerve stimulation and abolished the contraction on the injection of acetylcholine.

From the results of much work carried out between the original studies of Pal (23) in 1900, who first showed the mutual antagonistic action of physostigmine and curare, and those of Briscoe (24) in 1936, in her investigations of curarine and physostigmine in myasthenia gravis, considerable data have been obtained which show that curare acts by increasing the threshold of the muscle to acetylcholine, and that the administration of physostigmine and, more recently, neostigmine (prostigmine), permits the accumulation of acetylcholine to such an amount as to be active even when the threshold of the muscle is increased.

Koppanyi and Vivino (25), in their studies on the prevention and treatment of poisoning with d-tubocurarine chloride, showed that small doses of physostigmine or neostigmine would prevent paralysis and death in rabbits after a usually lethal dose of d-tubocurarine.

Harvey and Masland (26), investigating the action of curarizing preparations in man by recording the action potentials of the abductor digiti quinti muscle of the hand on stimulation of the ulnar nerve, found that a decrease occurred, after the intravenous injection of curare, in the action potentials when the subject showed signs of generalized weakness.

Studies on the Central Nervous System.—There have been numerous reports of the use of curare in various spastic diseases, and it was suggested that the beneficial results obtained in some cases might be explained on the basis of a central effect exerted by curare. In the studies by Hartridge and West (27) on dogs attacked by tetany which followed removal of the parathyroid glands, the authors observed that curare relieved the tetany without producing paralysis, and that this relief was not caused by a change in the irritability of the nerve-muscle unit as measured by the current needed for electrical stimulation of the nerve-muscle unit.

The most detailed studies of the effect of curare on the central nervous system are those of Feitelberg and Pick (28) and Pick and Unna (29) on the frog. Their procedure was to observe the effect of curare or d-tubocurarine chloride on the electro-encephalograms of both the normal and the pithed frog. Pick and his associates found that curare or d-tubocurarine chloride, when given in subparalytic or just paralytic doses, produced no changes from the control electro-encephalogram, but that if the dose of the curare preparation was in-

creased 50 to 100 per cent above that which would produce paralysis of the skeletal muscles, abolition of electrical potentials in the brain occurred, and that this central effect persisted considerably longer than the peripheral action. They also noted that the administration of prostigmine, which hastened the recovery of the skeletal nerve-muscle function, had no effect in restoring normal electrical activity in the brain. Thus, in frogs at least, curare and d-tubocurarine chloride exert both peripheral and central effects which are independent of each other.

Whitacre and Fisher (30) reported the use of solution of curare (intocostrin) among five patients in certain surgical procedures without the use of any general anesthetic agent. Two of the patients received a local anesthetic agent at the site of incision; curare was administered in a single dose or divided doses until complete muscular paralysis was produced and consciousness was lost; the operative procedure was completed while the patients received additional doses of curare and were maintained on artificial respiration. The third patient received an initial dose of 125 mg. of curare; this immediately caused complete muscular paralysis and loss of consciousness. Artificial respiration was maintained throughout the operation while additional doses of curare were necessary to keep the patient paralyzed. A total of 405 mg. of curare (intocostrin) was given during an hour and forty-five minutes. In two of the above cases normal respiratory activity was regained ten and forty-five minutes, respectively, before consciousness returned. In the final two cases curare was administered until all muscles except the diaphragm were paralyzed and the operation started. Later, these patients received cyclopropane to complete the operation, and after awakening from the cyclopropane anesthesia, they were able to tell of the pain they had experienced while they were under the influence of curare alone before the administration of cyclopropane was started.

These reports of cases by Whitacre and Fisher seem to parallel the work of Pick and his associates—that is, in neither instance did subparalytic doses of curare affect the central nervous system, and in both instances activity of skeletal muscles returned before activity returned in the central nervous system.

Harris, Pacella and Horwitz (31) made electro-encephalograms of patients who received curare before a preparation of pentamethylene tetrazol (metrazol). They found no significant changes that could be attributed to curare.

Studies on the Autonomic Nervous System.—There are two sites in the autonomic nervous system where curare may exert its effect on the transmission of impulses; that is, (1) at the ganglia and (2) at the effector cells. There is general agreement among various investigators that curare produces a depression of conduction through the autonomic ganglia, both the parasympathetic and sympathetic. Langley (32) in

1918 showed that the application of curare to autonomic ganglia abolished the conduction of electrical impulses from the preganglionic to the postganglionic fibers. In the autonomic ganglia, as in the voluntary nerve-muscle unit, curare blocks the transfer of electrical impulses at these cholinergic endings, but does not prevent the production and liberation of acetylcholine on stimulation of the preganglionic nerve fiber (33). The postganglionic nerve cells in a ganglion to which curare has been applied may be stimulated by other agents, such as potassium salts.

Luco and Mesa (34) reported their results of a study of the action of curare on the autonomic neuro-effector system in cats, as observed by the stimulation of preganglionic and postganglionic fibers innervating the muscles of the iris and nictitating membrane. The dose of curare used was that necessary to abolish respiratory activity in a cat anesthetized with 5-5-diallylbarbituric acid (dial). They found that curare abolished the pupillary response on stimulation of the preganglionic parasympathetic fibers to the eye. Likewise, curare prevented the contraction of the nictitating membrane on stimulation of the sympathetic preganglionic fibers. By the use of a dose of curare three to five times that necessary to produce paralysis of the skeletal muscles, they observed a partial reduction in effect when the postganglionic fibers to the iris were stimulated. However, when doses fourteen times that necessary to cause respiratory arrest were employed, there was no depression of effect on sympathetic postganglionic stimulation. Results of these studies support the original observations of Langley that curare blocks the transmission of impulses through the autonomic ganglia, and they go further to show than when curare is used in large doses the transmission of impulses from the parasympathetic postganglionic fiber to the effector cell is depressed.

In another report Luco and Altamirano (35) found that curare stopped the secretion from the submaxillary gland that routinely follows injection of acetylcholine.

Mautner and Luisada (36) investigated the effect of electrical stimulation of the vagus nerve on the heart of the dog, as reflected in the electrocardiogram, after curare had been administered. When a dose which was just below the full paralytic amount was used, the effect of vagal stimulation was greatly reduced; if the dose was sufficiently large to produce full curarization, then stimulation of the vagus nerve produced no changes in the heart as shown by electrocardiograms.

Gross and Cullen (37) have shown in their studies on dogs in which Thiry-Vella fistulas have been created that intocostrin or d-tubocurarine chloride, employed in a dose which will produce intercostal paralysis, routinely caused a reduction in tone and peristalsis of the intestine.

Ruskin, Ewalt and Decherd (38) reported an extensive study on the effect of curare (intocostrin) on the hearts of twenty-one human beings, as reflected in the electrocardiograms. Their procedure was

to make control records from five leads. Then, intocostrin in doses of from 1 unit to 1.6 units per kilogram of body weight was injected intravenously over a period of sixty seconds. Immediately afterward, and at frequent intervals thereafter, electrocardiograms, lead II, were made. At two to seven minutes after the injection, records were made in which all five leads were used. They were unable to detect any change in heart action caused by the curare used.

Harris, Pacella and Horwitz (31), Woolley (39) and Cleckley, Hamilton, Woodbury and Volpitto (40) have reported that the amount of curare that is ordinarily used in man has no depressing effect on the blood pressure.

Absorption and Excretion of Curare.—For the typical effect of curare to be observed, it is necessary that it be administered by the subcutaneous, intramuscular or intravenous route, through which effective concentrations can be reached. The rates of destruction and excretion of curare in the normal human being are such that the drug is noneffective when it is administered orally; however, if the renal vessels are ligated an effective concentration can be obtained by means of oral administration. Boehm (12) stated that the drug was eliminated by the kidney as shown by the curarizing properties of urine collected from a curarized animal.

Curare in Clinical Medicine.—The application of curare to problems in clinical medicine varies from that of relief from excessive contraction of skeletal muscles, as in tetanus or spastic disease, to the production of increased relaxation of abdominal muscles under light surgical anesthesia, to potentiating for diagnostic purposes the diminished ability of muscles for sustained repeated contractions in patients who have myasthenia gravis. Regardless of the end result desired in the use of curare in man, the mechanism by which these results are obtained is the same in all instances; that is, diminution of the effect of nerve stimuli on the voluntary or skeletal muscles, which diminution is thought to be brought about by the increase in threshold of the muscle for acetylcholine.

When curare is administered parenterally to man in a single large dose or in smaller repeated doses, there is a regular sequence in which the signs of complete curarization occur. First, the muscles of the eyelids and eyeballs are involved, resulting in a sensation of heaviness, ptosis, nystagmus and diplopia. Next, the facial muscles lose activity. Then the muscles of the neck and throat are affected, with resulting head drop and difficulty in speaking. Function of the muscles of the trunk and extremities is next depressed, and finally, the muscles of the diaphragm are paralyzed.

A generalization in relation to the use of curare in man should be made before a review is undertaken of the special conditions in which curare may be of benefit; that is, the effect of an overdose of curare can be corrected by the administration of physostigmine and also neostig-

mine (prostigmine), which, since the studies of Pal (23) in 1900, has been known to be a pharmacologic antidote for curare. Furthermore, by artificial maintenance of the patient's respiration for a few minutes, recovery usually will result from the rapid elimination of curare.

In any condition in which curare is to be used, the physician should have either physostigmine or neostigmine available for immediate intravenous injection. An efficient method for the maintenance of artificial respiration likewise should be at hand for instantaneous application. The only death which followed the use of curare to be reported in the literature occurred in a patient whose heart kept beating for six to seven minutes after paralysis of the skeletal muscles; this patient had had the benefit of artificial respiration but not that of neostigmine administered intravenously (41).

Curare in Tetanus, Rabies and Strychnine Poisoning.—In the earlier literature (2) there are reports of the use of curare to relieve the convulsions caused by tetanus, rabies and strychnine poisoning. Busch (42) wrote that Demme had treated twenty-two tetanic patients with curare, and that eight of these patients had survived.

Bremer (43) reported that experimental tetanus, produced by the intramuscular or subcutaneous injection of tetanus toxin, could be relieved readily by the injection of curare. Cole (44) obtained recovery of one of three tetanic patients to whom he administered curare. He administered four doses, each 32 mg., intravenously in a period of twenty-four hours, and the patient in question was free of symptoms for thirty-six hours. Subsequently, three more doses of 32 mg. each were administered over a period of twelve hours and the patient concerned made an uneventful recovery.

West (45) described in detail the procedure he used in the treatment of ten tetanic patients with curarine. He said he prefers the continuous intravenous drip method of administration of curarine. Although death was the ultimate outcome for nine of his ten patients, West did show that the frequency and severity of the convulsions could be reduced by the use of curarine. Bennett (46) was able to abolish the continuous tetanic convulsions of two patients by the use of curare. Cullen and Quinn (47) reported the use of curare in four cases of tetanus, with recovery in one case.

Curare in Spastic Diseases.—Bremer (43), in his discussion of tonus and contraction of skeletal muscles, stated that curare, administered in a dose of 0.25 mg. per kilogram of body weight, abolished the rigidity in decerebrate cats. He suggested that curare is effective in spastic diseases because it interrupts the continuous "involuntary" stimuli without abolition of the stimuli that occur in attempts at purposeful movements.

West (48), on the basis of previous results obtained by Hartridge and himself in the use of curare for relief of the spasticity of dogs which had parathyroid tetany (27), administered curare to thirty patients

who had rigidity of pyramidal tract and extrapyramidal tract origin. Although his results in the majority of these cases were unsatisfactory, there was in certain cases a selective removal of spasticity, as opposed to depression of voluntary activity, sufficient to make it desirable that further studies on this subject be carried out. West reported that 16 to 20 mg. of d-tubocurarine chloride, when administered subcutaneously to a patient who had disseminated sclerosis with spastic paraplegia, produced diminution of the spasticity without weakness, but that when doses of 50 mg. were employed, relaxation was produced in association with signs of generalized curarization.

Burman (49–51) presented extensive reports of his use of curare and erythroidine hydrochloride in spastic and dystonic states. The curare he used was prepared in a sterile, biologically standardized solution for intramuscular and intravenous use. The concentration was 5 mg. per cubic centimeter of solution (of such potency that 4.4 mg. per kilogram of body weight was fatal to 50 per cent of the frogs used for standardization). Since Pick and Unna (29) found that all frogs recovered from a dose of d-tubocurarine chloride of 3 mg. per kilogram of body weight, the curare used by Burman was very active.

Because of the uniform potency of the solution of curare, Burman was able to individualize the dose for his patients by starting to administer small doses and gradually increasing the dose until the desired effect was produced. Usually, a dose of 25 mg. administered intravenously produced satisfactory effects; if the solution was administered intramuscularly, the amount needed was about 50 mg. The dose in such cases, he thought, need not be greater than that required for paralysis of the muscles of the eyes and face. The maximal effect was noted immediately after intravenous injection, whereas after intramuscular injection the desired effect was obtained in twenty to thirty minutes, and signs of curarization persisted for three to four hours. From a clinical point of view, the spasticity was relieved for two to three days. Burman therefore repeated his injections at intervals of two to three days. Electromyographic studies of these patients showed the effects of curarization twenty-four hours after curare had been injected. There was no change in the blood pressure or pulse rate after curare had been administered to these patients.

Bennett (46) has used curare in a wide variety of cases of neurologic diseases. For seven children who had severe spastic paralysis the use of curare provided immediate relief of the spasticity; this relief persisted for a short time after the injection. The use of curare in some of the cases increased the favorable results that were expected from the orthopedic procedures and physiotherapy. The convulsions of a patient who had status epilepticus were prevented by the continuous intravenous administration of curare. The incoordinate movements of patients who had Huntington's chorea ceased and did not return for a few hours after the injection of curare.

Denhoff and Bradley (52) reported a detailed study of the use of curare in the form of intocostrin in the treatment of six children who had cerebral palsy. They found that the intramuscular route of administration gave the most satisfactory results in these cases. By careful preliminary observations a maintenance dose was established for each patient. This dose varied from 0.9 to 3.3 mg. per kilogram of body weight. The larger dose was necessary in the most severe generalized spastic condition, and as a rule the desired effects persisted for three to four days. The particular advantage in the use of curare in the spastic child was that it permitted an acceleration in the response to the muscle-training and educational program which are the basic factors in management of these patients.

Repeated studies of electrocardiograms, pulse rates and blood pressures of these subjects during their treatment with curare showed that curare in the amounts used produced no changes demonstrably different from those in the control observations.

Schlesinger (53) reported the administration of curare (intocostrin) to a patient who had transverse myelitis. He found that after curare had been injected intramuscularly the patient was able to carry out active exercise procedures. He also used a suspension of d-tubocurarine in peanut oil and myricin, and found that a single dose of this suspension given intramuscularly produced good relief of spasticity for three days without weakness of the muscles.

James and Braden (54) reported the use of curare for the treatment of spasms of the lower extremities of twelve patients who had paraplegia which followed transverse myelitis caused by wounds. They obtained best results when the curare was given intramuscularly in doses of 50 to 70 mg. four times daily. One of their patients received 156 injections (varying from 70 to 160 mg.) in a period of six weeks, and marked reduction in spasticity followed each dose. There was no reduction in the effect of an individual dose when administration of curare was repeated over a long period.

Curare in Metrazol and Electric Shock Therapy.—During the past eleven years the use of shock therapy and convulsions produced by the intravenous injection of metrazol or by an electric current for schizophrenia, involutional melancholia and other forms of psychosis has gained wide acceptance as a valuable procedure in these conditions. One of the most undesirable sequelae of this treatment is the relatively high frequency of occurrence of fracture of bones of the spinal column and extremities.

Bennett (55) reported that the incidence of fractures of the humerus or femur which accompany this form of treatment has been between 1.5 and 2 per cent, and that the incidence of dislocations has been as high as 17 per cent. The incidence of compression fractures of the vertebrae has ranged between 40 and 50 per cent. Easton and Som-

mers (56) reported that the incidence of fracture was 26 per cent in a series of 800 patients who received metrazol therapy.

Because of the high frequency of occurrence of fractures during convulsive treatment Bennett, who was using curare in the management of children who had spastic paralysis, tried curare as an agent to reduce the incidence of fractures during metrazol-induced convulsions. The dose which he employed was sufficient to produce paralysis of the extremities, and the calculated convulsion-producing dose of metrazol was given intravenously soon after the action of curare had become fully developed. The severity of the convulsion was greatly reduced by the administration of curare, but the therapeutic effect of the metrazol-induced shock was in no way reduced by the use of curare. By the time the patient recovered consciousness after the convulsion, the paralyzing effect of the curare had worn off.

In a more extensive paper, Bennett (8) reported the use of curare (intocostrin) in association with metrazol among 101 patients who received an average of 6.2 treatments each. In only one patient was there evidence of a fracture (a compression fracture of the seventh thoracic vertebra). The dose of intocostrin employed (containing 10 mg. per cubic centimeter) was about 5 cc. per 100 pounds (45.4 Kg.) Electroencephalographic records of patients receiving curare and metrazol did not differ from those of patients receiving metrazol alone.

Harvey and Masland (26) investigated the actions of curare, beta erythroidine and quinine methochloride and found that the severity of convulsions produced by metrazol was less after the administration of curare than after use of the other two agents.

Easton and Sommers (56) reduced the incidence of occurrence of fracture in shock therapy from 26.1 per cent, when metrazol was administered alone, to 5.8 per cent, when the use of metrazol was preceded by the administration of curare.

Goldman and Baber (57), Woolley, Jarvis and Ingalls (58), Cash and Hoekstra (59), Ebaugh (60), Bennett (61) and Heldt, Hurst and Dallis (62) reported on the administration of curare to patients immediately before the production of convulsions by electric shock. Curare was given about two minutes before the electric shock was produced. Curare reduced the severity of the convulsions and the danger of fracture.

(*To be concluded in July issue*)

REFERENCES

1. Gill, R. C.: Curare: Misconceptions Regarding the Discovery and Development of the Present Form of the Drug, Anesthesiology **7**: 14–23 (Jan.) 1946.
2. West, Ranyard: The Pharmacology and Therapeutics of Curare and Its Constituents, Proc. Roy. Soc. Med. **28** (pt. 1): 565–578 (Mar.) 1935.
3. Sollmann, Torald: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, Ed. 6, Philadelphia, W. B. Saunders Company, 1942, 1298 pp.

4. The Pharmacopoeia of the United States of America, Easton, Pennsylvania, Mack Printing Company, 1942, p. 670.
5. Folkers, Karl: Preliminary Studies in the Botanical Components of Tecuna and Java Curare, J. Am. Pharm. A. **27**: 689–693 (Aug.) 1938.
6. Gill, R. C.: The Geni in the Ampoule, Technology Rev. **43**: 297–298; 316–318 (May) 1941.
7. McIntyre, A. R., and King, R. E.: d-Tubocurarine Chloride and Choline Esterase, Science n. s. **97**: 69 (Jan. 15); Contraction of Denervated Muscle Produced by d-Tubocurarine, Science n. s. **97**: 516 (June 4) 1943.
8. Bennett, A. E.: Preventing Traumatic Complications in Convulsive Shock Therapy by Curare, J. A. M. A. **114**: 322–324 (Jan. 27) 1940.
9. Wintersteiner, O., and Dutcher, J. D.: Curare Alkaloids from ChondodendronTomentosum, Science n. s. **97**: 467–470 (May 21) 1943.
10. King, Harold: Curare Alkaloids. Part I. Tubocurarine, J. Chem. Soc., London, 1935 (pt. 2) pp. 1381–1389.
11. Gill, R. C.: White Water and Black Magic, New York, Henry Holt & Company, Inc., 1940, 369 pp.
12. Boehm, R.: Curare und Curarealkaloide. In Heffter, A.: Handbuch der experimentallen Pharmakologie, Berlin, Julius Springer, 1920, vol. 2, pp. 179–248.
13. Council of Pharmacy and Chemistry: New and Nonofficial Remedies, J. A. M. A. **129**: 517 (Oct. 13) 1945.
14. Wieland, Heinrich; Konz, Wilhelm, and Sonderhoff, Robert: Über das Curarin aus Calebassen-Curare, Ann. d. Chem. **527**: 160–168, 1937.
15. Brodie, B. C.: Experiments and Observations on the Different Modes in Which Death is Produced by Certain Vegetable Poisons, Phil. Tr., 1811, p. 194; 1812, p. 212.
16. Pelouze, J., and Bernard, C.: Recherches sur le Curare, Compt. rend. Acad. d. sc. **31**: 533–537 (Oct. 14) 1850.
17. Bernard, Claude: Analyse physiologique des propriétés des systèmes musculaire et nerveux au moyen du Curare, Compt. rend. Acad. d. sc. **43**: 824–829 (Nov. 3) 1856.
18. Kölliker, A.: Note sur l'action du Curare sur le système nerveux, Compt. rend. Acad. d. sc. **43**: 791–792 (Oct. 27) 1856.
19. Steiman, S. E.: Neuro-muscular Transmission in the Single Nerve and Muscle Fiber Preparation, Am. J. Physiol. **140**: 269–275 (Nov.) 1943.
20. Brinkman, R., and Ruiter, M.: Die humorale Übertragung des Skelettmuskelreizung eines ersten auf den Darm eines zweiten Frosches, Arch. f. d. ges. Physiol. **208**: 58–62, 1925.
21. Dale, H. H.; Feldberg, W., and Vogt, M.: Release of Acetylcholine at Voluntary Motor Nerve Endings, J. Physiol. **86**: 353–380 (May 4) 1936.
22. Brown, G. L.; Dale, H. H., and Feldberg, W.: Reactions of the Normal Mammalian Muscle to Acetylcholine and to Eserine, J. Physiol. **87**: 394–424 (Sept.) 1936.
23. Pal, J.: Physostigmin ein Gegengift des Curare, Zentralbl. f. Physiol. **14**: 255–258 (Aug.) 1900.
24. Briscoe, Grace: The Antagonism Between Curarine and Prostigmin and Its Relation to the Myasthenia Problem, Lancet **1**: 469–472 (Feb. 29) 1936.
25. Koppanyi, Theodore, and Vivino, A. E.: Prevention and Treatment of d-Tubocurarine Poisoning, Science n. s. **100**: 474–475 (Nov. 24) 1944.
26. Harvey, A. M., and Masland, R. L.: Actions of Curarizing Preparations in the Human, J. Pharmacol. & Exper. Therap. **73**: 304–311 (Nov.) 1941.
27. Hartridge, H., and West, Ranyard: Parathyroid Tetany in Dogs, and Its Abolition by Curare, Brain **54**: 312–319 (Sept.) 1931.
28. Feitelberg, Sergei, and Pick, E. P.: Action of Curare on the Brain of the Frog, Proc. Soc. Exper. Biol. & Med. **49**: 654–656 (Apr.) 1942.
29. Pick, E. P., and Unna, K.: Effect of Curare and Curare-like Substances on Central Nervous System, J. Pharmacol. & Exper. Therap. **83**: 59–70 (Jan.) 1945.
30. Whitacre, R. J., and Fisher, A. J.: Clinical Observations on the Use of Curare in Anesthesia, Anesthesiology **6**: 124–130 (Mar.) 1945.
31. Harris, M. M.; Pacella, B. L., and Horwitz, W. A.: A Study of the Use of Curare in Metrazol Convulsant Therapy with Some Electroencephalographic Observations, Psychiatric Quart. **15**: 537–543 (July) 1941.
32. Langley, J. N.: On the Stimulation and Paralysis of Nerve Cells and Nerve Endings. Part II. Paralysis by Curari, Strychnine and Brucine and Its Antagonism by Nicotine, J. Physiol. **52**: 247–266 (Oct.) 1918.
33. Brown, G. L.: Transmission at Nerve Endings by Acetylcholine, Physiol. Rev. **17**: 485–513 (Oct.) 1937.

34. Luco, J. V., and Mesa, J.: Acción del curare en los sistemas neuroefectores autonómicos, Ciencia **2**: 298–299 (Sept. 25) 1941.
35. Luco, J. V., and Altamirano, M.: A Comparison of Atropine and Curare as Antagonists to Acetylcholine, Am. J. Physiol. **139**: 520–524 (Aug.) 1943.
36. Mautner, Hans, and Luisada, Aldo: Antagonistic Effect of Asphyxia to Curare Paralysis of the Vagus Nerve, J. Pharmacol. & Exper. Therap. **72**: 386–393 (July) 1941.
37. Gross, E. G., and Cullen, S. C.: The Action of Curare on the Smooth Muscle of the Small Intestine and on the Blood Pressure, Anesthesiology **6**: 231–238 (May) 1945.
38. Ruskin, Arthur; Ewalt, Jack, and Decherd, George: The Electrocardiogram of Curarized Human Patients, Dis. Nerv. System **4**: 335–341 (Nov.) 1943.
39. Woolley, L. F.: Immediate Circulatory and Respiratory Effects of Convulsive Shock (Curare Protected Metrazol and Electric Shock), J. Nerv. & Ment. Dis. **100**: 1–23 (July) 1944.
40. Cleckley, Hervey; Hamilton, W. P.; Woodbury, R. A., and Volpitto, P. P.: Blood Pressure Studies in Patients Undergoing Convulsive Therapy, South. M. J. **35**: 375–380 (Apr.) 1942.
41. Charlton, G. E.; Brinegar, W. C., and Holloway, O. R.: Curare and Metrazol Therapy of Psychosis; Report of a Fatal Case, Arch. Neurol. & Psychiat. **48**: 267–270 (Aug.) 1942.
42. Busch: Quoted by West, Ranyard (2).
43. Bremer, Frédéric: The Tonus and Contracture of Skeletal Muscles, Arch. Surg. **18**: 1463–1490 (Apr.) 1929.
44. Cole, Leslie: Treatment of Tetanus by Curare, Brit. M. J. **1**: 126 (Jan. 19) 1935.
45. West, Ranyard: Intravenous Curarine in the Treatment of Tetanus, Lancet **1**: 12–16 (Jan. 4) 1936.
46. Bennett, A. E.: Clinical Investigations with Curare in Organic Neurologic Disorders, Am. J. M. Sc. **202**: 102–112 (July) 1941.
47. Cullen, S. C., and Quinn, C. S.: The Use of Curare in the Treatment of Tetanus; Case Report, Surgery **14**: 256–260 (Aug.) 1943.
48 West, Ranyard: Curare in Man, Proc. Roy. Soc. Med. **25**: 1107–1116 (May) 1932.
49. Burman, M. S.: Clinical Experiences with Some Curare Preparations and Curare Substitutes, J. Pharmacol. & Exper. Therap. **69**: 143–148 (June) 1940.
50. Burman, M. S.: Therapeutic Use of Curare and Erythroidine Hydrochloride for Spastic and Dystonic States, Arch. Neurol. & Psychiat. **41**: 307–327 (Feb.) 1939.
51. Burman, M. S.: Curare Therapy for the Release of Muscle Spasm and Rigidity in Spastic Paralysis and Dystonia Musculorum Deformans, J. Bone & Joint Surg. **20**: 754–756 (July) 1938.
52. Denhoff, Eric, and Bradley, Charles: Curare Treatment of Spastic Children; Preliminary Report, New England J. Med. **226**: 411–416 (Mar. 12) 1942.
53. Schlesinger, E. B.: Intocostrin Used in Spasticity Following Transverse Myelitis, In: Curare. Intocostrin, New York, E. R. Squibb & Sons, 1946, p. 252.
54. James, D. F., and Braden, Spencer: The Use of Curare in the Treatment of Spastic Paralysis, J. Neurosurg. **3**: 74–80 (Jan.) 1946.
55. Bennett, A. E.: Curare: a Preventive of Traumatic Complications in Convulsive Shock Therapy, Am. J. Psychiat. **97**: 1040–1060 (Mar.) 1941.
56. Easton, N. L., and Sommers, Joseph: Vertebral Fractures in Metrazol Therapy With and Without the Use of Curare as a Supplement, J. Nerv. & Ment. Dis. **99**: 256–263 (Mar.) 1944.
57. Goldman, Douglas, and Baber, E. A.: Electric Convulsion Therapy in Psychoses, Am. J. M. Sc. **203**: 354–359 (Mar.) 1942.
58. Woolley, L. F.; Jarvis, J. R., and Ingalls, G. S.: On the Use of Curare in Modifying Convulsive Shock, J. Nerv. & Ment. Dis. **96**: 680–693 (Dec.) 1942.
59. Cash, P. T., and Hoekstra, C. S.: Preliminary Curarization in Electric Convulsive Shock Therapy, Psychiat. Quart. **17**: 20–34 (Jan.) 1943.
60. Ebaugh, F. G.: A Review of the Drastic Shock Therapies in the Treatment of the Psychoses, Ann. Int. Med. **18**: 279–296 (Mar.) 1943.
61. Bennett, A. E.: The Present Status of Convulsive Shock Therapy, J. Nerv. & Ment. Dis. **98**: 23–30 (July) 1943.
62. Heldt, T. J.; Hurst, D. D., and Dallis, N. P.: Electric Shock Therapy in a General Hospital, Arch. Int. Med. **73**: 336–340 (Apr.) 1944.

AN ATTEMPT TO PROLONG SYMPATHETIC BLOCK * † WITH BROMSALIZOL IN POLYETHYLENE GLYCOL

MEREL H. HARMEL, M.D., LEROY D. VANDAM, M.D., AND AUSTIN LAMONT, M.D. ‡

Baltimore, Maryland

Received for publication January 20, 1947

FOR many diagnostic and therapeutic blocks of the sympathetic nervous system the transient effect of procaine and similar agents is adequate. There are, however, some instances in which it is desirable to obtain a more prolonged effect than is possible with procaine. Neither alcohol nor local analgesic agents in oil have proved to be entirely satisfactory. In 1944 Lee, Macht and Pierpont (1, 2) reported that bromsalizol, 4 per cent, in peanut oil, was a nontoxic and relatively nonirritating agent which would produce sympathetic block for several days or weeks and sometimes for as long as four months. The variation in the duration of the blocks was attributed to the low diffusibility of the peanut oil solution and it was emphasized that the effectiveness of the block depended on how close to the ganglion the solution was deposited.

In some 60 sympathetic blocks performed with bromsalizol in peanut oil we found that many of the patients exhibited signs of block for a longer period than one would expect had procaine alone been injected, although this factor was not controlled by previous injections of procaine alone. Curiously enough, few of these patients exhibited changes in the electrical resistance of the skin (9) for more than a day or two, although other signs of block (increased temperature, anhidrosis, absence of pain, and so forth, were still present.

Although we expect to continue to use 4 per cent bromsalizol in peanut oil for sympathetic blocks, our difficulty in obtaining a consistently prolonged effect with this agent led us to seek a more concentrated and a more diffusible solution. We chose bromsalizol, 20 per cent in polyethylene glycol-400.

Bromsalizol, first described by Macht and Dunning (3) in 1934, is a monobrom hydroxy-benzyl alcohol very soluble in alcohol, ether, and the high molecular weight glycols, but soluble in water only to 0.5 per cent. Its maximum solubility in peanut oil is 4 per cent. In preliminary studies on animals (4), we found that polyethylene glycol-400 and bromsalizol, 20 per cent, in polyethylene glycol-400 were relatively nontoxic (see also 5, 6, 7, 8), could produce prolonged block of small nerve fibers, and caused an appreciable amount of tissue irritation in

* From the Department of Surgery, Division of Anaesthesia, The Johns Hopkins University and Hospital.

† This study was aided by a grant from Hynson, Westcott and Dunning.

‡ Present address: 2 Warrenton Road, Baltimore 10, Maryland.

rabbits. It was thought that the prolongation of block in animals was sufficient to warrant a trial of this new combination of drugs in human beings.

MATERIAL

Of 9 patients selected for block with the 20 per cent bromsalizol, 6 had pain or ulcers associated with changes in the peripheral vascular bed of the lower extremity, 2 had acute thrombophlebitis, and 1 had an ulcer and edema of obscure origin. Only lumbar sympathetic blocks were performed on these patients (table 1).

TABLE 1

LUMBAR SYMPATHETIC BLOCK WITH 20 PER CENT BROMSALIZOL IN POLYETHYLENE GLYCOL-400

Pt. No.	Indication for Block	Evidence of Block			Complications Following Block
		Increased Skin Resistance		Other Evidence Later	
		Immediate	Later		
1	Pain in leg; diabetic neuritis	Yes	Slight after 24 hours	Anhidrosis and increased temperature of skin for at least 3 days	Pain in flank; fever
2	Pain in leg; arteriosclerosis	Yes	None when tested 8 days later	Anhidrosis and increased temperature of skin for at least 6 days	Pain in flank; fever
3	Pain in leg	Yes	For 5 days	Yes	None
4	Ulcer and edema of leg; sickle cell anemia	Yes	None when tested 8 days later	Anhidrosis and increased temperature of skin for at least 6 days	Pain in flank
5	Pain and ulcer of leg; arteriosclerosis	Yes	For at least 8 days	Yes	Slight pain in flank
6	Pain in leg following frostbite	Yes	For at least 3 days	Yes	None
7	Pain and ulcer of leg; arteriosclerosis	Yes	None when tested 3 days later	Anhidrosis and increased temperature of skin for at least 3 days	Pain in flank; fever, and bronchopneumonia
8	Acute thrombophlebitis	No	None	None	None
9	Acute thrombophlebitis	Yes	For at least 7 days	Yes	None

TECHNIC

The patients were given 0.1 Gm. of pentobarbital by mouth thirty minutes or so before the block. After placing the needle, 1 or 2 cc. of 1 per cent procaine or metycaine was injected. If there was no sign

of block within five minutes, the needle was reintroduced and another small injection made. The bromsalizol solution was not administered until it was thought that the needle was as close to the sympathetic chain as possible. In some instances the needle was introduced four or five times before injecting the bromsalizol solution. Usually 4 or 5 cc. of the 20 per cent solution was used.

The criteria for successful block were: (a) a change in the resistance of the skin to the passage of an electric current as measured by Richter's "dermometer" (9, 10); (b) gross changes in temperature, and (c) anhidrosis.

RESULTS

The results of the blocks are summarized in table 1. In patients 3, 5, 6 and 9, a definite prolongation of the skin's increased electrical resistance was obtained after block, accompanied by increased temperature of the skin and anhidrosis. In patients 1, 2, 4 and 7 there was no prolongation of increased skin resistance, although other signs of block were present for three to six days. Patient 8 showed no signs of a sympathetic block at any time.

Further use of this solution was deemed inadvisable because of the development within twenty-four hours of serious complications in 5 of the 9 patients, and because of the findings at operation on 4 of the patients.

Pain.—Severe pain in the flank developed in patients 1, 2, 4 and 7. Patients 2 and 4 did not return to the hospital for six days because of the severity of the pain. The pain was not characteristic of nerve root irritation and there were no sensory changes.

Fever.—There was an increase in temperature to 103.6 F. within twenty-six hours in patients 1 and 7. The fever subsided in forty-eight to seventy-two hours. We do not believe that the bronchopneumonia which developed in patient 7 was related to the block.

Tissue Irritation.—Surgical section of the lumbar sympathetic was attempted after the block in patients 2, 4, 5 and 6. In each case the surgeon noted that the tissues in the region of the sympathetic chain were distorted by inflammation and scarring. The tissues were friable and identification was difficult. In patient 5 there was doubt whether the ganglia had been excised because they could not be found in the tissues removed at operation and skin resistance patterns after operation were characteristic of regeneration of sympathetics rather than of a sympathectomy. The operation was apparently successful in the other 3 patients, but in 1 patient the surgeon noted at operation that the ureter was constricted by a dense band of scar tissue, a finding subsequently confirmed by intravenous pyelograms.*

* Ten of the 60 patients in whom block was carried out with bromsalizol, 4 per cent, in peanut oil subsequently had the sympathetic chain and ganglia excised. Although the surgeons observed some mild scarring and inflammation around the sympathetics, this was not sufficient to interfere with the operative procedure and the identification of the ganglia.

COMMENT

The presence of pain and fever after the injection of the solution and the appearance of the tissues at operation led us to believe that 20 per cent bromsalizol in polyethylene glycol-400 is too irritating to human tissues to warrant its further trial. Had opportunity offered, we intended to study solutions containing lower concentrations of bromsalizol and polyethylene glycol-400 which might well prove more useful than the bromsalizol, 4 per cent, in peanut oil.

SUMMARY

Encouraging but inconsistent results in the use of 4 per cent bromsalizol in peanut oil to produce prolonged sympathetic block led to the trial of a more diffusible solution, 20 per cent bromsalizol in polyethylene glycol-400. Although this latter solution does prolong sympathetic block, its irritation of tissues makes it unsuitable for clinical use in the concentrations used.

We wish to record our gratitude to the personnel of Dr. Richter's laboratory for their cooperation in determining the electrical resistance of the skin in these patients.

REFERENCES

1. Lee, F. C.; Macht, D. I., and Pierpont, R. Z.: Preliminary Report on Method for Lengthening the Effect of a Sympathetic Nerve Block, Bull. Johns Hopkins Hosp. **74**: 119–120 (Feb.) 1944.
2. Lee, F. C.; Macht, D. L., and Pierpont, R. Z.: Use of Bromsalizol in Lengthening the Effect of Sympathetic Nerve Block, Am. J. M. Sc. **209**: 314–324 (Mar.) 1945.
3. Macht, D. I., and Dunning, F.: Pharmacologic and Therapeutic Study of Bromsalizol or Mono-brom-saligenin, J. Lab. & Clin. Med. **20**: 127–140, 1934.
4. Vandam, L. D.; Lamont, A., and Harmel, M. H.: Study of the Long-acting Local Anesthetic Properties of Bromsalizol in Oil and in Polyethylene Glycol-400. To be published.
5. Friedman, M. H. F.: Vehicle for the Intravenous Administration of Fat-soluble Hormones, J. Lab. & Clin. Med. **29**: 530–531 (May) 1944.
6. Smyth, H. F., Jr.; Seaton, J., and Fischer, L.: Single Dose Toxicity of Some Glycols and Derivatives, J. Indust. Hyg. & Toxicol. **23**: 259–268 (June) 1941.
7. Smyth, H. F., Jr.; Carpenter, C. P.; Shaffer, C. B.; Seaton, J., and Fischer, L.: Some Pharmacological Properties of Polyethylene Glycols of High Molecular Weight ("Carbowax" Compounds), J. Indust. Hyg. & Toxicol. **24**: 281–284 (Nov.) 1942.
8. Reid, M. R., and Altmeier, W. A.: Peroxide Ointments, Ann. Surg. **118**: 741–750, 1943.
9. Richter, C. P., and Woodruff, B. G.: Changes Produced by Sympathectomy in the Electrical Resistance of the Skin, Surgery **10**: 957–970, 1940.
10. Shumacker, H. B., Jr.: Value of Skin Resistance Studies in Determining Accuracy of Procaine Injections of Sympathetic Nerves, Surgery **11**: 949–961 (June) 1942.

INTRASPINAL SEGMENTAL ANESTHESIA: A PRELIMINARY REPORT * †

MEYER SAKLAD, M.D., CLEMENT S. DWYER, M.D., SANFORD KRONENBERG, M.D., EDMUND NEVES, M.D. AND MORRIS SORKIN, M.D.

Providence, R. I.

Received for publication November 4, 1946

SERIOUS sequelae still result from intraspinal injections of anesthetic agents. The hazards of low blood pressure, respiratory paralysis and damage to the subarachnoid nerve elements, particularly the cauda equina, still exist. If it were possible to limit anesthesia to the operative field and to use anesthetic agents in more dilute solutions and in smaller doses, certain undesirable effects of spinal anesthesia might be avoided. It is the purpose of this paper to describe a new technic of spinal anesthesia in which the extent of sensory, motor and autonomic effects may be limited. This segmental anesthesia can be produced by dilute solutions of anesthetic drugs in very low dosage.

In 1932, Kirschner (1) described a technic for the production of an intraspinal segmental anesthesia. With the patient in lateral head-down position, the spinal fluid in the lower end of the dural canal was withdrawn and replaced by air. A hypobaric nupercaine solution was floated on the spinal fluid beneath the air. Further injections of air would move the anesthetic agent cephalad. Phillipides (2) modified this technic by omitting the injection of air. Fay and Gotten (3) were able to obtain segmental anesthesia by using two needles, one in the lumbar subarachnoid space and the other in the cisterna magna. Vehrs (4) and others obtained segmental anesthesia by doing high spinal punctures.

With the advent of the catheter technic for fractional administration of drugs for spinal anesthesia and with the knowledge of the efficacy of dilute solutions, a more satisfactory method of segmental spinal anesthesia has been evolved.

TECHNIC

The patient is placed in a lateral decubitus position with the table horizontal. A spinal puncture is performed at the second or third lumbar interspace with a 16 gauge Huber-pointed needle. The opening of the needle is in proper position to point a catheter passing through

* Read before the New England Society of Anesthesiologists, Boston, Mass., September 17, 1946.

† From the Department of Anesthesia, Rhode Island Hospital, Providence, R. I.

it in a cephalad direction when the notch in the hub is turned toward the head of the patient. A 1:2000 solution of pontocaine hydrochloride is prepared by diluting 0.5 cc. of 1 per cent pontocaine with 9.5 cc. of spinal fluid. A 3½ French Tuohy continuous spinal catheter, graduated in 1 and 5 cm. markings, containing a soft stainless steel stilet, is inserted into a spinal needle. At times, difficulty is encountered in passing the catheter beyond the tip of the needle. By steadying the catheter with one hand and slightly withdrawing the

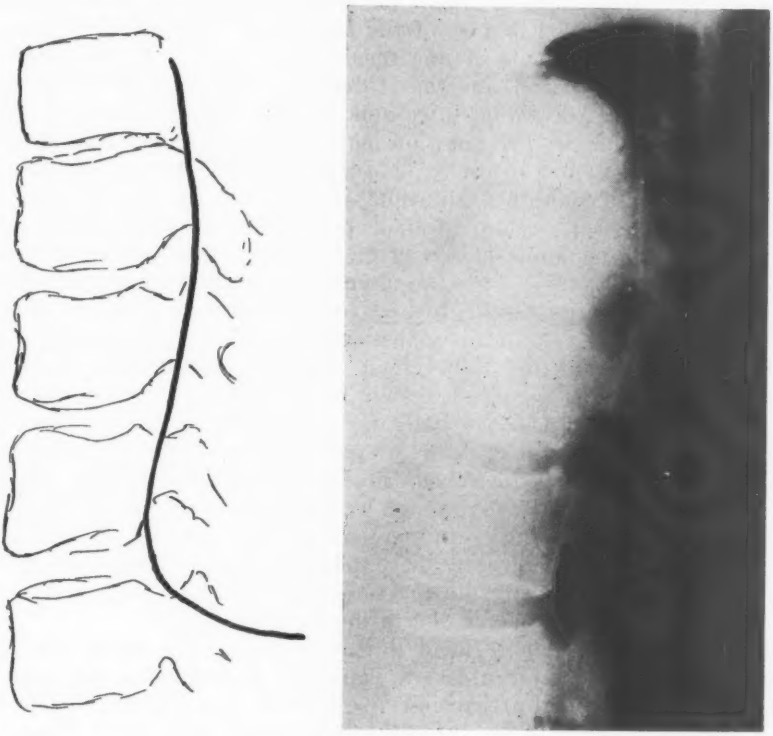


FIG. 1. Catheter properly placed.

needle with the other, the catheter can be advanced with ease. Occasionally paresthesias are elicited. If there is resistance to the passage of the catheter through the subarachnoid space, force should not be used. The catheter is gently pushed cephalad until it has been inserted a distance of 25 to 35 cm. as measured at the hub of needle (fig. 1). The length of catheter within the subarachnoid space is determined by subtracting the length of the needle (9.5 cm.) from this figure. The needle should not be rotated with the catheter in place, and no attempt

should be made to withdraw the catheter once it has passed through the tip of the needle. The sharp edge of the Huber point may sever the catheter or shave off pieces from its side unless the needle is first removed from the patient's back. After removal of the needle the stilet is withdrawn from the catheter, and a 10 cc. syringe, containing the pontocaine solution, is attached to the catheter by a snug-fitting needle. The catheter is fastened to the skin by adhesive tape. The patient is turned supine, and the syringe is brought up behind his shoulder. In order to prevent a back-flow of spinal fluid into the syringe, a piece of adhesive tape is fastened along the barrel and piston.

An initial dose of 2 to 4 cc. of the pontocaine solution (1 to 2 mg.) is injected and the levels of anesthesia determined. If the catheter has been properly placed, anesthesia develops rapidly with sharp lines of demarcation. Additional injections of 1 or 2 cc. are made if anesthesia is inadequate. The solution leaves the tip of the catheter with considerable force, and a rapid rate of injection will cause wider spread of the agent, with consequent dilution. Slow injection provides greater assurance that the concentration of pontocaine at the desired level within the subarachnoid space will more nearly approach that of the solution in the syringe. Thus, an almost true volumetric displacement is obtained. Injections of 0.5 to 1 cc. (0.25 to 0.5 mg.) at thirty minute intervals adequately maintain anesthesia during long operative procedures. Additional doses are given when an indication exists, such as when relaxation for closure can be improved or when visceral sensation is annoying to the patient. An attempt is made, however, to distinguish between discomfort or pain arising in the operative field and restlessness resulting from inadequate premedication, oxygen want, position or nausea. Although we recognize the frequent need for complementary or supplementary agents during spinal anesthesia, we have purposely premedicated these patients lightly and have given minimal quantities of drugs during the operation to evaluate the action of intraspinal segmental anesthesia more accurately.

The operating table is level during induction of anesthesia and throughout the operation unless a change is required for the surgical procedure. No special precautions are necessary to prevent the spread of the agent cephalad since the solution is nearly isobaric. From the standpoint of technic, we do not hesitate to place the patient in steep Trendelenburg position at any time. An intravenous infusion is started at the ankle after the patient is warned that he will feel a needle prick. The upper and lower limits of the anesthetized area are repeatedly determined during the operation by pinching the skin with an Allis clamp to demonstrate loss of sensation in segmental dermatomes. A descending upper level indicates that an additional injection of pontocaine is necessary. Persistent motor control of the lower extremities is demonstrated by having the patient move his toes or feet and raise his knees against the hand of the anesthetist.

RESULTS

This preliminary report includes our first 24 cases of intraspinal segmental anesthesia. In all of these the anesthesia was given for abdominal surgery. In 20 cases anesthesia was satisfactory. In two cases it was necessary to supplement with nitrous oxide-oxygen because of visceral sensation. Four cases were technical failures owing to faulty placement of the catheter. In one of these the catheter was curled upon itself within the subarachnoid space (fig. 2), and in another

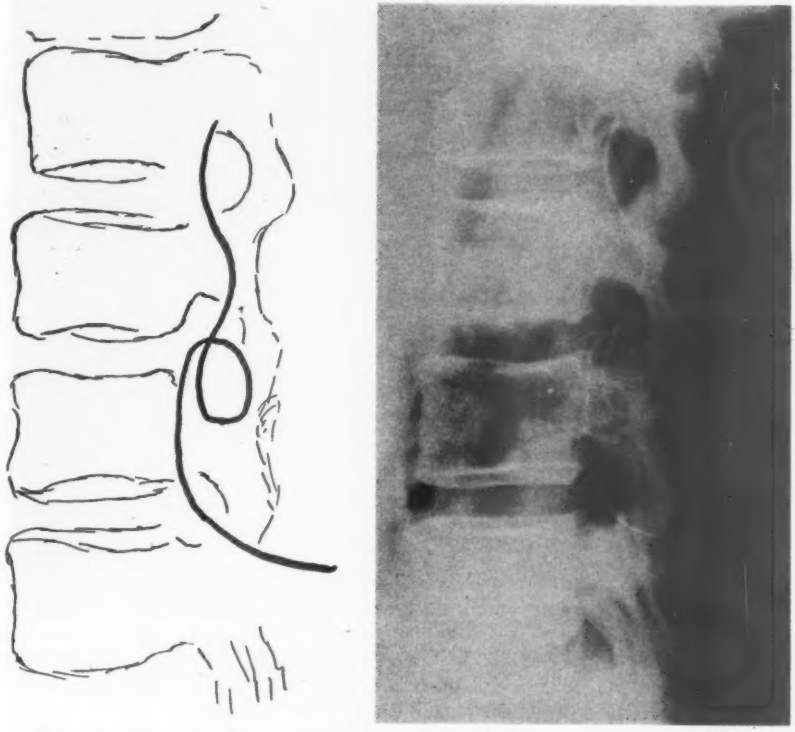


FIG. 2. Improper placement of catheter. The catheter was inserted without stilet. It has curled upon itself and has not advanced sufficiently far cephalad for satisfactory anesthesia.

the tip of the catheter had turned and was directed caudad (fig. 3). These catheters had been inserted without stilets. We now employ fine, stainless steel stilets to make certain that the catheters will pass directly cephalad within the subarachnoid space. In the third case, although roentgenologic examination was not made, it was believed that the catheter had not been advanced for a sufficient distance. The

fourth failure resulted from the inadvertent use of an ordinary ureteral catheter in place of the Tuohy catheter. The ureteral catheter has three lateral openings near its tip, whereas the Tuohy catheter has a single hole located at its extreme end. The latter provides a directional flow (cephalad) of the injected anesthetic solution.

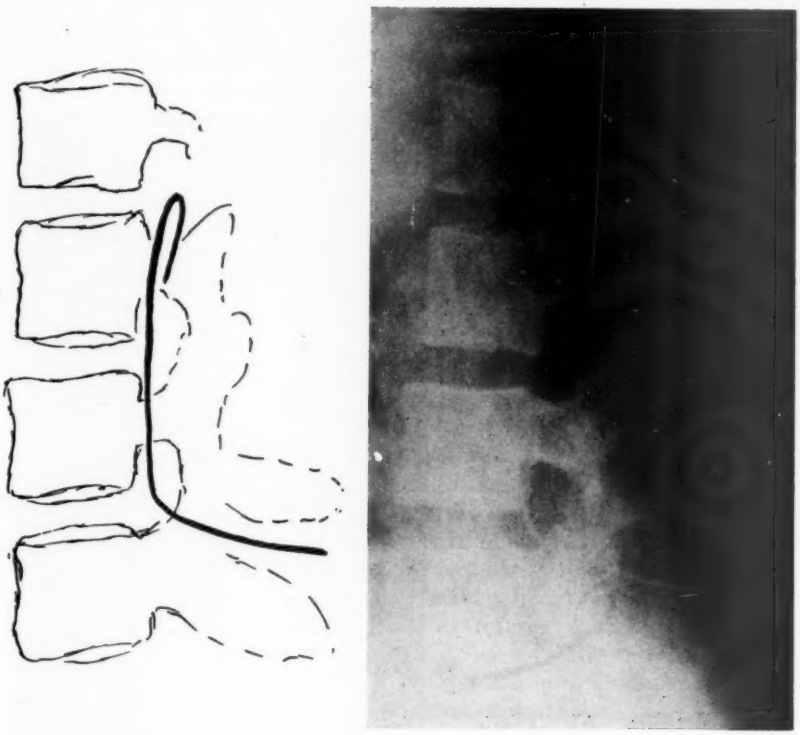


FIG. 3. Improper placement of catheter. The catheter was inserted without stilet. It has reversed its direction and too low an anesthesia was obtained.

Paresthesias were occasionally produced by the needle or catheter during their insertion, but neurologic sequelae have not appeared in these patients.

The following are résumés of cases of intraspinal segmental anesthesia.

Figure 4 is the record of a 37-year-old, obese man with a large incisional hernia. Puncture was done at the third lumbar interspace. The length of catheter within the subarachnoid space was 14 cm. The patient tolerated well the repair of an extensive defect. A segmental distribution of anesthesia was illustrated by the fact that it was necessary for the surgeon to infiltrate the

scrotum with procaine to insert a drain while anesthesia of the abdomen was still entirely satisfactory. The operation lasted four hours and fifteen minutes. A total dose of 5.5 mg. of pontocaine was injected.

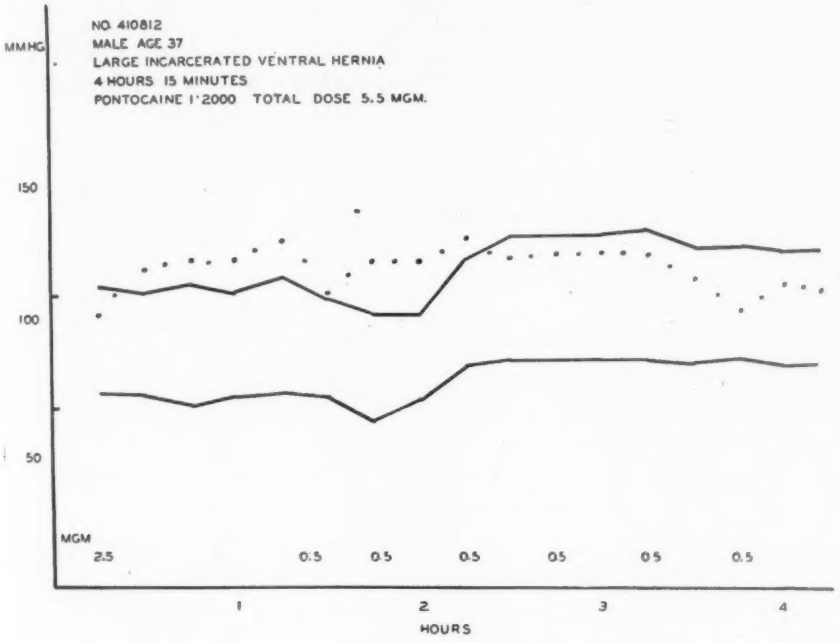


FIG. 4. Man, age 37; repair large incarcerated ventral hernia. Duration 4 hours 15 minutes; total dose pontocaine 5.5 mg.

Figure 5 represents the longest anesthesia of the series. A 50-year-old man was operated on because of carcinoma of the pancreas. Puncture was done at the second lumbar interspace. The length of catheter within the subarachnoid space was 20 cm. The operation required six hours and fifty minutes. An extensive resection of the duodenum and pancreas was performed. A total dose of 6 mg. of pontocaine was given. The patient died on the second postoperative day because the hepatic artery had been accidentally ligated.

Figure 6 is the chart of a 49-year-old man with a perforated peptic ulcer. Puncture was done at the second lumbar interspace. The length of catheter within the subarachnoid space was 17 cm. Satisfactory anesthesia for closure of the perforation was produced by the injection of 5 cc. (2.5 mg.) of pontocaine and 1 cc. (0.5 mg.) twenty minutes later. After one hour and thirty minutes of surgery, anesthesia was present between the sixth thoracic and third lumbar segments.

Figure 7 represents a 70-year-old man on whom cholecystectomy was performed. Puncture was done at the third lumbar interspace. The catheter was inserted 24 cm. within the subarachnoid space. The maximum extent of

anesthesia was from the first to the twelfth thoracic segments. The operation lasted one hour and forty minutes. The total dose of pontocaine was 4 mg.

Figure 8 is the chart of a 70-year-old woman on whom cholecystectomy was performed. Puncture was done at the second lumbar interspace. The length of catheter within the subarachnoid space was 15 cm. An initial injection of 5 cc. (2.5 mg.) produced anesthesia between the third thoracic and second lumbar segments. After fifty-five minutes an additional 2 cc. (1 mg.) was given. The operation was completed fifty-five minutes later. Forty-five minutes

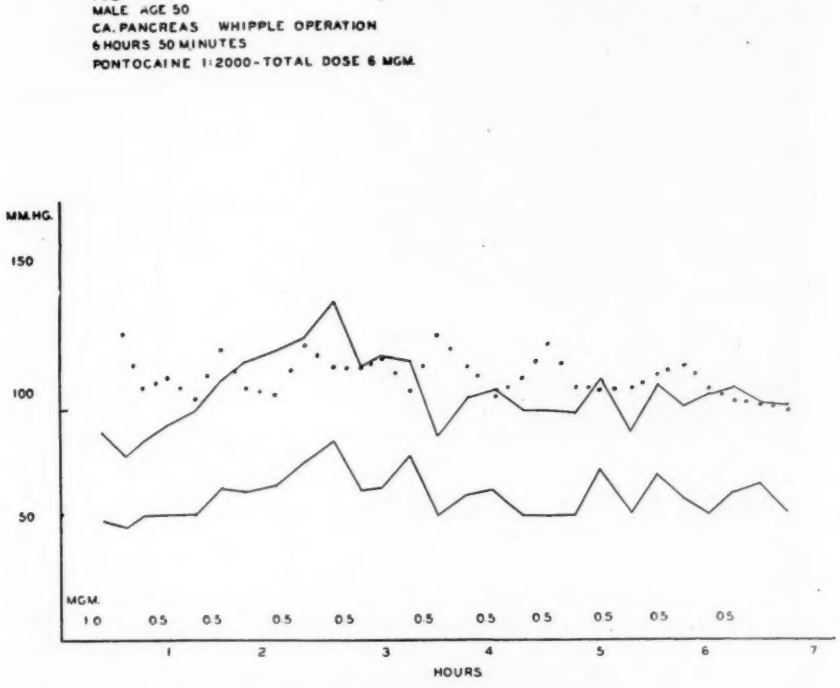


FIG. 5. Man, age 50; Whipple operation. Duration 6 hours 50 minutes; total dose pontocaine 6.0 mg.

after the patient left the operating room, anesthesia was present between the seventh thoracic and first lumbar. The total dose of pontocaine was 3.5 mg.

Figure 9 is the record of a 63-year-old woman. Puncture was done at the third lumbar interspace. The length of catheter within the subarachnoid space was 15 cm. The repair of a strangulated umbilical hernia lasted one hour and ten minutes, and required only 1 mg. of pontocaine. Anesthesia extended from the eighth to the twelfth thoracic segments.

Figure 10 illustrates that the lower level of anesthesia can be too high for the operation. Puncture was done at the second lumbar interspace. The catheter was advanced 21 cm. within the subarachnoid space. An initial injec-

tion of 2 cc. (1 mg.) produced anesthesia between the fourth and eighth thoracic segments. The surgeon was unable to proceed because of inadequate anesthesia at the operative site. Two additional injections of 2 cc. each failed to produce the desired result. The catheter was then withdrawn 5 cm., and 2 cc. again injected. The lower level promptly changed to the twelfth thoracic. A strangulated, internal hernia was repaired. The operation lasted one hour and ten minutes. A total dose of 4 mg. was given.

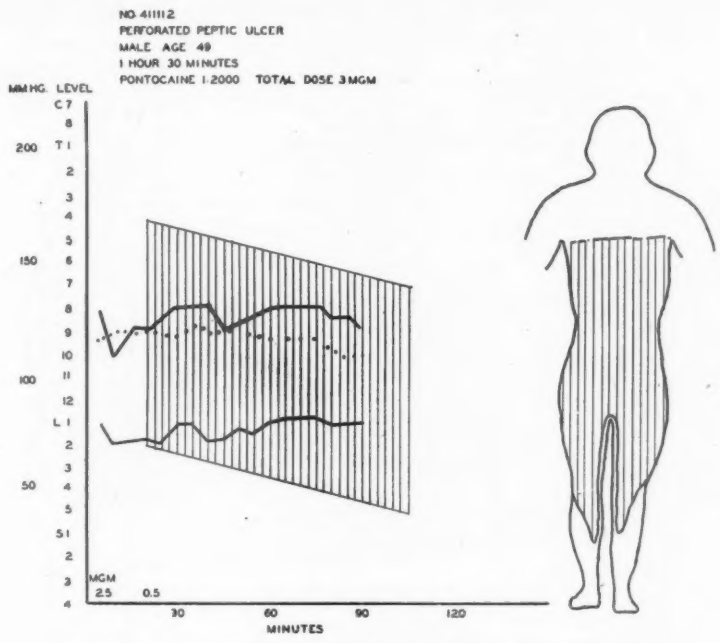


FIG. 6. Man, age 49; suture perforated peptic ulcer. Duration 1 hour 30 minutes; total dose pontocaine 3 mg.

DISCUSSION

Certain technical and theoretical considerations of intraspinal segmental anesthesia produced by a 1:2,000 pontocaine solution will be discussed in relation to first, the agent, and second, the method.

AGENT

The solution of anesthetic drug in this dilution (5 mg. of pontocaine hydrochloride in 10 cc. of spinal fluid) is more nearly isobaric and isotonic than the solutions which are ordinarily employed for spinal anesthesia. Its hydrogen-ion concentration deviates little from that of spinal fluid. These characteristics will be considered individually because they are novel to agents employed in spinal anesthesia.

Dilution.—Lindemulder (5) described damage in the spinal cord and nerve roots of patients dying soon after having received a subdural anesthetic. Nicholson and Eversole (6) reported a series of cases with neurologic sequelae following spinal anesthesia. Van Lier (7), Wossidlo (8), Spielmeyer (9) and Davis and his associates (10) showed that toxic degenerative changes of the subarachnoid nerve elements may occur following spinal anesthesia. Lundy (11), in an experimental study, concluded that the concentration of the agent is as im-

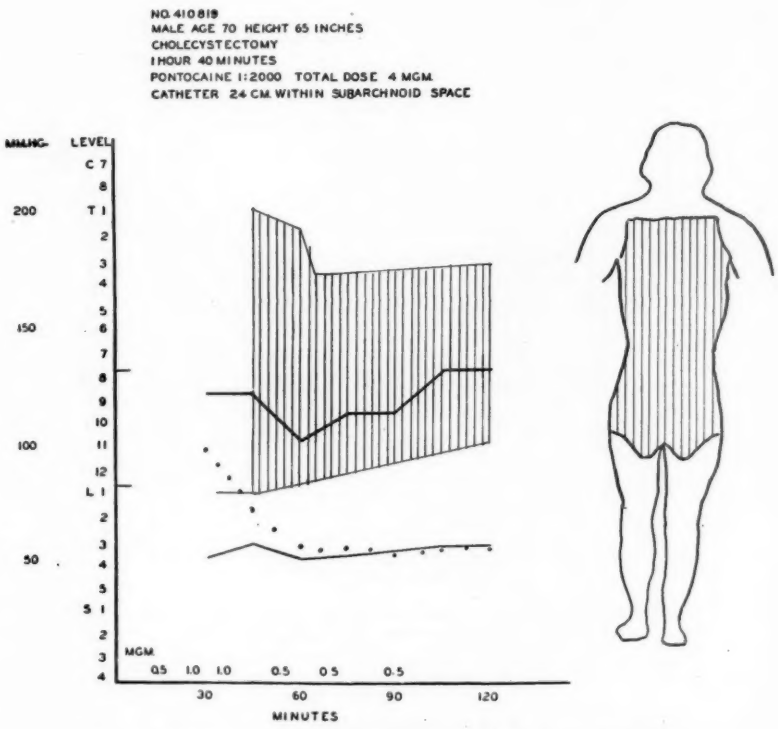


FIG. 7. Man, age 70; cholecystectomy. Duration 1 hour 40 minutes; total dose pontocaine 4.0 mg.

portant as the total dose in producing permanent paralysis. Other experiments (12, 13) in animals demonstrated that those portions of the cord and nerves which are exposed to the highest concentration of the drug are most severely affected. Livingstone and her co-workers (14) reported findings of nerve involvement in cases of death following spinal anesthesia. She stated, "Probably there is in every case some toxic reaction produced in nervous tissue by agents used for spinal anesthesia but, in the majority of cases, repair of this damaged tissue

is apparently rapid and complete. Occasionally, due to some local or general condition of the patient, recovery is retarded or impeded and therefore we have a few, but widely varied, neurologic sequelae which may be temporary or permanent."

Paraplegia, quadriplegia, cauda equina syndrome, neuropathy, myelopathy, encephalopathy and meningitis have been described by numerous observers. Nicholson and Eversole (6) stated that "In the concentration employed, most spinal anesthetic drugs have a toxicity but little short of that which would produce paralysis in a higher percentage of cases."

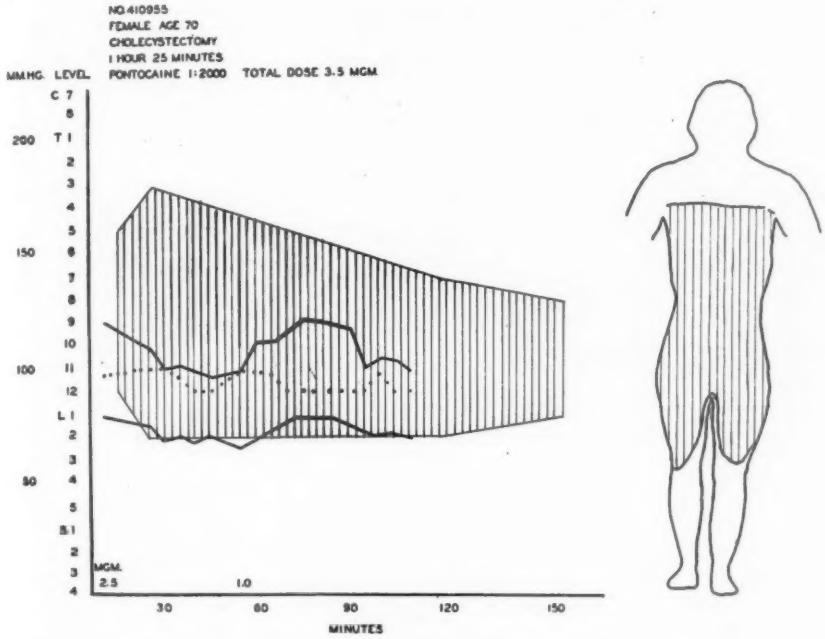


FIG. 8. Woman, age 70; cholecystectomy. Duration 1 hour 25 minutes; total dose pontocaine 3.5 mg.

Because of these pathologic changes and sequelae which have been described, it is desirable to inject into the subarachnoid space the lowest possible concentrations of anesthetic agents that will produce satisfactory anesthesia. A concentration of 1:2000 pontocaine is an effective anesthetic solution only when it is deposited in the immediate vicinity of the nerve roots. This is accomplished by injecting it through a catheter. The necessity of employing more concentrated solutions as when the injection is made into the lumbar region is obviated.

Tonicity.—Certain physical and chemical properties of anesthetic solutions may be partly responsible for organic changes in nerve tissues and meninges. Irritative and degenerative changes may result when tissues are exposed to solutions of different tonicity. Tainter (15) has pointed out in his studies of local anesthetic agents that hypertonic solutions cause shrinkage of cells and hypotonic solutions cause swelling of cells. Wagner (16) has demonstrated in dogs that intrathecal hypotonic solutions are much more harmful than isotonic or hypertonic

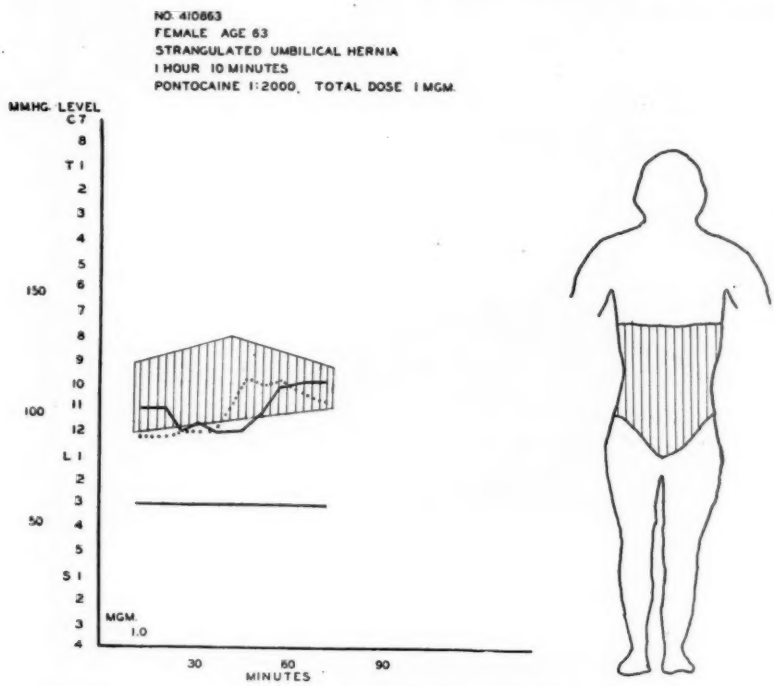


FIG. 9. Woman, age 63; repair strangulated, umbilical hernia; duration 1 hour 10 minutes; total dose pontocaine 1.0 mg.

solutions. *In vitro* experiments on tissue slices show that the tonicity of the medium will alter normal metabolism (17). Therefore, it is advisable to use an anesthetic solution as nearly isotonic as possible.

Baricity.—In the ordinary technics, a hyperbaric solution is injected, and the patient is turned supine. The primary effect is on the posterior roots, and there is a wider area of sensory loss than of motor paralysis. It becomes difficult for the anesthetist to assure himself of the extent of muscle relaxation. When a hypobaric solution is injected and the patient is turned supine, a greater number of anterior roots are affected

and there is a wider area of motor paralysis than of skin anesthesia. The anesthetist may not be aware of a high level of intercostal paralysis. On the other hand, after the injection of hyperbaric and hypobaric solutions and the patient is turned prone, there is predominantly a motor and sensory loss, respectively.

The use of pontocaine in small amounts in spinal fluid makes an anesthetic solution which is nearly isobaric. The minute quantity of the solute exerts a negligible effect on the specific gravity. Such a

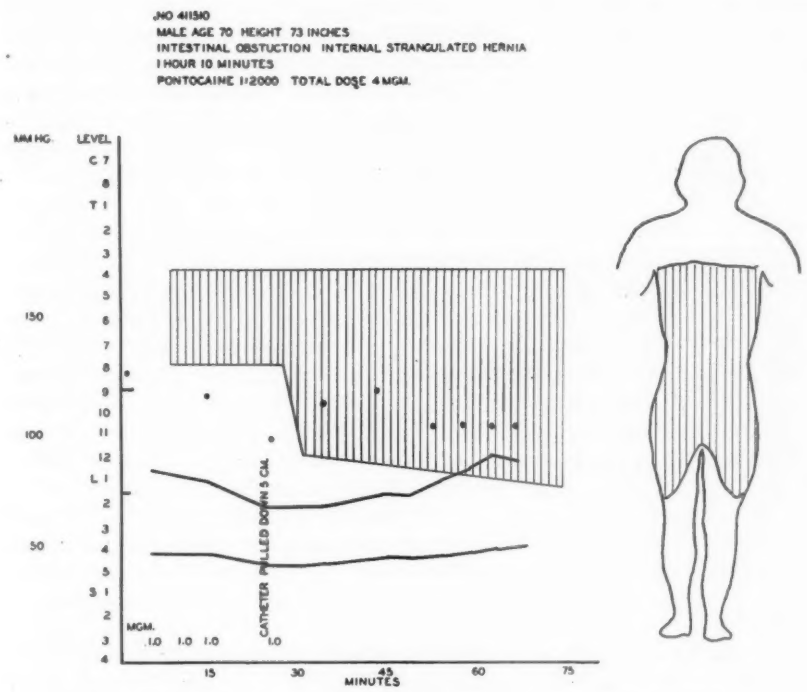


FIG. 10. Man, age 70; reduction internal, strangulated hernia; duration 1 hour 10 minutes; total dose pontocaine 4.0 mg.

solution, deposited in a selected area of the subarachnoid space, has little tendency to spread cephalad or caudad and to involve adjacent segments of the cord and its nerves. Regardless of the position of the patient, the isobaric solution bathes corresponding anterior and posterior nerve roots simultaneously and thus achieves a more nearly equal distribution of motor paralysis and sensory loss.

Hydrionicity.—A chemical factor which may influence the toxicity of an anesthetic agent is the pH of its solution. Tainter (15) stated that highly acid and highly alkaline local anesthetic solutions are ob-

jectionable because they may cause damage to cells. Weaver and Kitchin (18) have demonstrated morphologic changes in cats' sciatic nerves after injection of solutions which are hypotonic and which have an abnormal hydrionicity. The pH of tissue is about 7.4, while solutions of the commonly employed anesthetic drugs are definitely acid. One per cent pontocaine hydrochloride in saline solution, with acetone bisulfite as a stabilizing agent, has a pH of 3.4, while a 1 per cent aqueous solution of crystals of pontocaine hydrochloride has a pH of 5.5. Spinal fluid is used as the diluent in the preparation of 1:2000 pontocaine and, because of its buffer systems, the solution is as nearly isohydrionic as possible. The pH of spinal fluid is reduced about 0.15 in making the 1:2000 solution with 1 per cent pontocaine-acetone bisulfite solution. The pH alteration in making 1:2000 solution of pontocaine crystals in spinal fluid is about 0.02. The anesthetic solution which comes in contact with nerve tissues approaches physiologic values in its specific gravity, tonicity and hydrogen-ion concentration.

METHOD

The standard technics for spinal anesthesia require solutions of anesthetic agents which differ considerably in specific gravity from that of spinal fluid. To obtain diffusion of the agent inside the subarachnoid space, a relatively concentrated solution is injected into the lumbar region so that its concentration will still be effective when it reaches the nerve roots of distant levels. By advancing a catheter within the subarachnoid space, one is able to bathe the specific roots directly with a weak yet effective concentration of the drug without depending on diffusion. Further dilution of the pontocaine solution by spinal fluid *in situ* results in its failure to produce a complete motor or sensory block. Thus the extent of spread of segmental anesthesia depends almost entirely upon the volume of solution injected at any one time. The deposition of a given volume of this solution about selected nerve roots results in a segmental spinal anesthesia with well demarcated upper and lower limits. Since there is little spread of the anesthetic solution in a caudad direction, lumbar, sacral and coccygeal nerves may not be blocked during an intraspinal segmental anesthesia.

The method will be evaluated first, from the standpoint of persistent somatic motor activity and, second, from that of persistent autonomic activity.

Motor.—It is interesting to speculate as to whether the blood pressure fall will be less pronounced with this method than with the usual technics of spinal anesthesia. The cause of hypotension during spinal anesthesia is still uncertain. It is difficult to discuss how the mechanisms involved might be modified by a segmental technic without omitting many important considerations. Since this report represents a small number of cases, no valid conclusion can be drawn from our clinical results.

It has been claimed that muscle paralysis is one of the contributing factors to the fall in blood pressure. Seevers and Waters (19) stated that skeletal muscle paralysis is one of the factors in the chain of events that leads to hypoxia, hypotension and respiratory paralysis. The theory of stagnation of blood in the postarteriolar bed has been defended by Smith and his associates (20). They stated that there is a pooling of blood in the paralyzed musculature causing a decreased venous return, a diminution in the stroke volume of the heart and a fall in arterial blood pressure. Intraspinal segmental anesthesia for upper abdominal surgery limits the amount of muscular paralysis, for, in every case, it is intended that motor control in the lower extremities shall persist. The muscles of the lower limbs are innervated by nerves which arise below the first lumbar segment of the spinal cord. It is not necessary to block lumbar nerves for surgery of the upper abdomen.

Respiratory paralysis is the greatest single hazard of spinal anesthesia. This type of respiratory failure results from action of anesthetic agents on anterior nerve roots supplying the upper intercostal muscles and the diaphragm. The possibility of its occurrence from uncontrolled spread of the agent is markedly reduced in an intraspinal segmental anesthesia. The technic affords greater control over the anesthetic solution since it is placed directly into the vicinity of selected nerve roots. The hazard is further reduced because the dilution of the agent approaches its minimal effective concentration. Somatic motor fibers are more resistant to the effects of anesthetic drugs than are sensory fibers. Emmett (21) demonstrated that motor paralysis occurs after loss of sensation during the induction of spinal anesthesia. Solkow (22), Sarnoff and Arrowood (23) showed that pain sensation can be abolished without producing motor paralysis by intrathecal injections of procaine. Diffusion of 1:2000 pontocaine within the subarachnoid space will result in a concentration insufficient to produce motor paralysis.

Phlebothrombosis may occur less frequently after the use of intraspinal segmental anesthesia since patients are able to move their legs during the operation and the immediate postoperative period. In most cases of phlebothrombosis, clots begin to form in the smaller veins of the foot and calf. Trauma of surgery predisposes to intravascular clotting, and the period of immobilization of the limbs during the ordinary spinal anesthesia adds stagnation of venous flow. It has been said that many cases of phlebothrombosis begin on the operating table. According to Homans (24) "Although the proper combination of factors can surely occasion thrombosis at any time, the early hours and days (after operation) are especially liable to it." In view of the above, it may be of distinct advantage to maintain muscular tone in the lower extremities. This is one aim of segmental spinal anesthesia.

Autonomic.—Opposed to the theory of the cause of blood pressure fall already discussed is the concept of paralysis of the vasoconstrictor

fibers in the anterior spinal nerve roots. Ferguson and North (25) stated that the degree of depression of blood pressure is in direct ratio to the number of white rami anesthetized. Co Tui (26) conceived the fall of blood pressure to be the result of somatic and visceral vasodilation. Koster (27) studied the hypotension of spinal anesthesia in normal, unoperated man and concluded that the hypotension is primarily due to arteriolar dilatation. Sarnoff and Arrowood (23), employing the technic of "differential spinal block," stated that the reduction of blood pressure is entirely the result of blocking of sympathetic fibers. Many vasoconstrictor fibers to the lower extremities leave the spinal cord below its twelfth thoracic segment. In the majority of cases of this series complete loss of sensation did not extend below the twelfth thoracic dermatome. Some central vasomotor control in the lower extremities should persist in these patients and the degree of blood pressure fall may be less pronounced. Studies to determine the extent of persistent sympathetic activity during segmental spinal anesthesia have not been completed.

The question of sympathetic innervation of skeletal muscle and its effect on muscle tone has not been settled. Kuntz (28) has reviewed this problem and has concluded that there is evidence to support the contention that sympathetic system activity tends to increase tone of muscles and that sympathectomy is followed by a reduction in muscle tone. This must be considered in evaluating the advantages of segmental spinal anesthesia. The maintenance of normal muscle tone should influence venous return from the extremities, thereby supporting cardiac output, limiting the extent of blood pressure fall, and reducing the incidence of phlebothrombosis.

Anesthesia confined to nerve roots above those which innervate the urinary bladder may lead to a reduced incidence of postoperative urinary disturbances. The mechanism of voluntary micturition is dependent upon a cortical control over certain somatic and autonomic reflexes within the spinal cord (fig. 11). Sympathetic control of the bladder is mediated through the upper lumbar spinal segments by way of the hypogastric nerves. Sympathetic impulses are inhibitory to the detrusor muscle and motor to the trigone, internal sphincter and the smooth muscle of the proximal portion of the urethra. The parasympathetic innervation arises in the first four sacral segments and reaches the bladder through the pelvic nerves. Parasympathetic impulses are motor to the detrusor muscle and inhibitory to the internal sphincter. The pudendal nerves comprise the somatic nerve supply and control the external sphincter. Afferent fibers essential for reflex movements of the bladder are contained in the pelvic nerves, those for movements of the urethra in the pudendal nerves. Sympathetic nerves carry no afferent fibers necessary for the important reflex mechanisms. Denning (29) has shown that section of either the pudendal or hypogastric nerves or both has little effect on voluntary urination, while

section of the pelvic nerves brings about profound functional and trophic disturbances of the bladder. Although premedication, the supine position, trauma of surgery and pain may produce urinary retention during the postoperative period, urinary disturbances may be less frequent following intraspinal segmental anesthesia than after the usual spinal anesthesia.

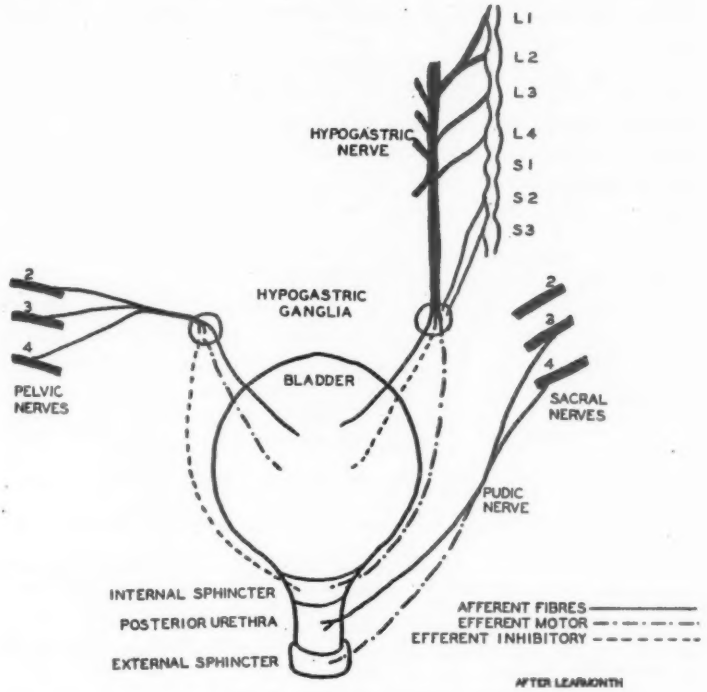


FIG. 11. Innervation of urinary bladder.

SUMMARY

1. A practical and simple method of obtaining a segmental distribution of spinal anesthesia is presented. A limited number of spinal nerve roots are bathed by an anesthetic solution within the subarachnoid space.

2. A solution of pontocaine hydrochloride in a dilution of 1:2000 is injected through a fine catheter which has been passed cephalad within the subarachnoid space a distance of 15 to 25 cm.

3. A 1:2000 dilution of pontocaine is of sufficient concentration to produce satisfactory spinal anesthesia by this technic.

4. The total dose of pontocaine is a small fraction of that ordinarily required for spinal anesthesia.

5. The following practical and theoretical advantages of intraspinal segmental anesthesia have been discussed:

a. The dilute solution of pontocaine in spinal fluid may be considered to be nearly isotonic, isobaric and isohydrionic. Local toxic effects and neurologic sequelae are, therefore, less likely to result.

b. The accurate deposition of such a weak solution of anesthetic agent within the subarachnoid space reduces the hazard of respiratory paralysis.

c. Persistence of motor power in the lower extremities may result in a more efficient return flow of blood to the heart and may have a beneficial effect on the systemic circulation during anesthesia.

d. Maintenance of muscle tone in the legs may result in a decreased incidence of phlebothrombosis.

e. Postoperative urinary disturbances may be less common.

Note.—Since submitting this report, we have found that the 1:2000 concentration of pontocaine in spinal fluid produced inadequate analgesia in an occasional patient. For this reason, we now employ a 1:1000 solution. The pH of spinal fluid is reduced about 0.18 using 1 per cent pontocaine-acetone bisulfite solution and 0.03 using pontocaine crystals to make the latter preparation.

REFERENCES

1. Kirschner, M.: Spinal Zone Anesthesia, Placed at Will and Individually Graded, Surg., Gynec. & Obst. **55**: 317–329 (Sept.) 1932.
2. Phillipides: Spinal Anesthesia, Segmental Block, Nupercaine Anesthesia, Arch. Klin. Chir. 189, 1937.
3. Fay, T., and Gotten, N.: Controlled Spinal Anesthesia; Its Value for Establishing Appropriate Levels for Chordotomy, Arch. Neuro. & Psychiat. **30**: 1276–1281 (Dec.) 1934.
4. Vehrs, J. R.: Spinal Anesthesia, St. Louis, C. V. Mosby Co., 1934.
5. Lindemulder, F. G.: Spinal Anesthesia, Its Effect on the Central Nervous System, J. A. M. A. **99**: 210–212 (July 16) 1932.
6. Nicholson, M. J., and Eversole, U. H.: J. A. M. A., in press.
7. Van Lier, E. H.: Histologischer Beitrag zur Rückenmarks-anästhesie, Beitr. z. Klin. Chir. **54**: 413, 1907.
8. Wossidlo, E.: Experimentelle Untersuchungen über Veränderungen der nisslschen Granula bei der Lumbalanästhesie, Arch. f. Klin. Chir. **86**: 1017, 1908.
9. Spielmeyer, E.: Veränderungen des Nervensystems nach Stovain-Anästhesie, München med. Wchnschr. **55**: 1629, 1908.
10. Davis, L.; Haven, H.; Givens, J. H., and Emmett, J.: Effects of Spinal Anesthetics on the Spinal Cord and Its Membranes, J. A. M. A. **97**: 1781 (Dec. 12) 1931.
11. Lundy, J. S.; Essex, H. E., and Kernohan, J. W.: Experiments with Anesthetics. IV. Lesions Produced in the Spinal Cord of Dogs by a Dose of Procaine Hydrochloride Sufficient to Cause Permanent and Fatal Paralysis, J. A. M. A. **101**: 1546–1550 (Nov. 11) 1933.
12. MacDonald, A. D., and Watkins, K. H.: An Experimental Investigation into the Cause of Paralysis Following Spinal Anesthesia, Brit. J. Surg. **25**: 879–883, 1937–1938.
13. Klose, H., and Vogt, H.: Physiologische und Anatomische Untersuchungen zur Lumbalanästhesie and zur Frage Ihren Klinischen Verwertbarkeit, München Med. Wchnschr. **56**: 505–507, 1909.
14. Light, G.; Sweet, W. H.; Livingstone, H., and Engel, R.: Neurological Changes Following Spinal Anesthesia, Surgery **7**: 138–156 (Jan.) 1940.

15. Tainter, M. L.: Summary of Studies on the Optional Composition of Local Anesthetic Solutions, Anesthesiology **2**: 489–502 (Sept.) 1941.
16. Wagner, J. C.; Sievers, R. F.; Bennett, A. L., and McIntyre, A. R.: Spinal Anesthesia in the Dog, J. Pharmacol. & Exper. Therap. **68**: 437–453 (April) 1940.
17. Rapport, D., and Canzanelli, A.: Personal communication.
18. Weaver, H. M., and Kitchin, P. C.: Observations on Peripheral Nerves Following Local Injections of 1) Isotonic Solutions of Varying pH and 2) "Iso-pH" Solutions of Varying Tonicity, J. Dent. Res. **17**: 431 (Dec.) 1938.
19. Seevers, M. H., and Waters, R. M.: Respiratory and Circulatory Changes During Spinal Anesthesia, J. A. M. A. **99**: 961–968 (Sept.) 1932.
20. Smith, H. W.; Rovenstine, E. A.; Goldring, W.; Chasis, H., and Ranges, H. A.: The Effects of Spinal Anesthesia on the Circulation in Normal Unoperated Man with Reference to the Autonomy of the Arterioles and Especially Those of the Renal Circulation, J. Clin. Investigation **18**: 319–341 (May) 1939.
21. Emmett, J. L.: Subarachnoid Injections of Procaine Hydrochloride. The Quantitative Effects of Clinical Doses on Sensory Sympathetic and Motor Nerves, J. A. M. A. **102**: 425–432 (Feb. 10) 1934.
22. Solkow, M. L.: Selective Sensory (Posterior) Spinal Root Block; a Preliminary Report, Anesth. & Analg. **24**: 261–262 (Nov.-Dec.) 1945.
23. Sarnoff, S. J., and Arrowood, J. G.: Differential Spinal Block, Surgery **20**: 150–159 (July) 1946.
24. Homans, J.: Circulatory Diseases of the Extremities, New York, Macmillan Co., 1939.
25. Ferguson, L. K., and North, J. P.: Experimental Spinal Anesthesia, Surg., Gynec. & Obst. **54**: 621–634 (Apr.) 1932.
26. Co Tui, F. W.: Further Studies in Subarachnoid Anesthesia, Anesth. & Analg. **13**: 183–192 (Sept.-Oct.) 1934.
27. Koster, H.: Blood Pressure Changes During Spinal Anesthesia in Non-operative Cases, Arch. Surg. **45**: 596–605 (Oct.) 1942.
28. Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1945.
29. Denning, H.: Untersuchungen über die Innervation der Harnblase und des Mastdarmes, Ztschr. f. Biol. **80**: 239–254, 1924.

AWARD OF SWEDISH ORDER OF VASA TO DR. RALPH M. WATERS

His Majesty, the King of Sweden, recently honored Dr. Ralph M. Waters of Madison, Wisconsin, by making him a knight of the Order of Vasa, First Class. Mr. G. Oldenburg, Swedish consul-general, of the Swedish Consulate in Chicago, made the presentation at a dinner in Madison, March 17, 1947. The dinner was attended by the executive committee of the Medical School, University of Wisconsin and many of Dr. Waters' colleagues from the State of Wisconsin General Hospital. This award was granted in appreciation of Dr. Waters' public services to Sweden in the training of three Swedish doctors in the field of Anesthesiology.

Dean William S. Middleton presided as toastmaster. Following pertinent and accurate complimentary remarks concerning Dr. Waters, he introduced the Swedish consul-general. Mr. Oldenburg reviewed the history of the Order of Vasa and made known the gratitude of the Swedish medical profession to Dr. Waters for public service to them by training their first anesthesiologists. In Dr. Waters' acceptance of the medal, he characteristically pointed out that such an honor was not purely a personal one, but one which included the fine spirit of cooperation and "teamwork" which exists among the medical faculty at Wisconsin. Dr. Eric Nilsson, the third Swedish doctor to study in Madison, on behalf of himself and his predecessors, thanked Dr. Waters for his many kindnesses and wise counsel.

ANESTHESIA: XXVI. THE DETERMINATION OF ETHERS IN BLOOD WITH SPECIAL REFERENCE TO METHYL n-PROPYL ETHER * †

DOROTHY V. KIBLER, M.A.

Baltimore, Md.

Received for publication November 22, 1946

INTRODUCTION

IN studying the clinical usefulness of new inhalation anesthetic agents, it is desirable to correlate the degree of anesthesia with the concentration of the agent in the blood of the patient. When the compound being studied is volatile and capable of oxidation, the determination of blood concentrations has been carried out in the following manner.

1. Vaporize the compound.
2. Pass the vapors into a known quantity of suitable oxidizing reagent.
3. Determine how much of the oxidizing agent is consumed in the reaction.
4. From the stoichiometric relation in the reaction between anesthetic and oxidizing agent, calculate the amount of anesthetic.

This general scheme was adapted to the determination of blood concentrations of a new anesthetic agent, methyl n-propyl ether (metopryl). The method used in this laboratory is based in part on the work of Andrews, Potter, Friedemann, and Livingstone (1).

THEORETICAL

A potassium dichromate-sulfuric acid solution, 5 cc. 0.100 N $K_2Cr_2O_7$ and 20 cc. of 75 per cent H_2SO_4, was used as the oxidizing agent. The reaction of methyl n-propyl ether in this medium proceeds as follows:

1. $C_3H_7OCH_3 + 2H_2SO_4 \rightarrow C_3H_7OSO_3H + CH_3OSO_3H + H_2O$
2. $3C_3H_7OSO_3H + 3CH_3OSO_3H + 10H_2SO_4 + 4K_2Cr_2O_7 \rightarrow 3C_2H_5COOH + 3HCOOH + 4Cr_2(SO_4)_3 + 16H_2O + 4K_2SO_4$

The propionic acid undergoes no further oxidation, but the formic acid will continue:

3. $3HCOOH + K_2Cr_2O_7 + 4H_2SO_4 \rightarrow K_2SO_4 + Cr_2(SO_4)_3 + 3CO_2 + 7H_2O$

* From the Department of Pharmacology, Medical School, University of Maryland, Baltimore.

† The expense of this investigation was defrayed in part by a grant from the Ohio Chemical & Manufacturing Co., Cleveland.

Combining equations 2 and 3 we have:

4. $3C_3H_7OSO_3H + 3CH_3OSO_3H + 14H_2SO_4 + 5K_2Cr_2O_7 \rightarrow 3C_2H_5COOH + 3CO_2 + 5Cr_2(SO_4)_3 + 5K_2SO_4 + 23H_2O$

Since the two alkyl sulfonic acids are derived from one original ether molecule, the total quantity of ether referred to by equation 4 is 3 moles. It will be seen that 5 moles of $K_2Cr_2O_7$ are required to oxidize the sulfonic acids derived from this quantity of ether. This ratio of 3 moles of ether to 5 moles of $K_2Cr_2O_7$ is the basis for the stoichiometric calculation of ether concentrations.

TITRATION

It was found that the titration of solutions containing such strong sulfuric acid was not reliable owing to the indefinite and variable end-point. Even test titrations of known quantities of $K_2Cr_2O_7$ in the presence of 20 cc. of 75 per cent H_2SO_4 gave erroneous results. In order to avoid this difficulty, an excess of solid $BaCl_2.2H_2O$ was added to aqueous sulfuric acid solutions containing a known amount of $K_2Cr_2O_7$. When the $SO_4^=$ ions had all been removed as solid $BaSO_4$, reproducible iodometric titrations with $Na_2S_2O_3$ were made possible, and the results checked the known amount of $K_2Cr_2O_7$ originally used. The end-point, in the presence of the precipitated $BaSO_4$, was the change from a light powder blue to chalky white. The equations for this reaction are as follows:

1. $H_2SO_4 + BaCl_2 \rightarrow BaSO_4 + 2HCl$
2. $K_2Cr_2O_7 + 6KI + 14HCl \rightarrow 8KCl + 2CrCl_3 + 7H_2O + 3I_2$
3. $2Na_2S_2O_3 + I_2 \rightarrow 2NaI + Na_2S_4O_6$

CALCULATION

The titration with standardized $Na_2S_2O_3$, 0.01 N, shows the amount of 0.100 N $K_2Cr_2O_7$ still present in the oxidizing solution, which is calculated as follows:

1. (ml. thiosulfate) (N thiosulfate) = (X)(0.1) where X = the number of ml. of 0.100 N $K_2Cr_2O_7$ solution.
   (5 — X) therefore is the number of ml. of 0.100 N $K_2Cr_2O_7$ solution used in the oxidation of the ether vapors.

The number of moles of $K_2Cr_2O_7$ per ml. in a 0.100 N solution is 1.67×10^{-5}. Therefore, letting M represent number of moles of ether,

2. $\frac{(5 - X)(1.67 \times 10^{-5})}{M} = \frac{5}{3}$ since the molar ratio between $K_2Cr_2O_7$ and ether is 5 to 3.

Rearranging, and multiplying by the molecular weight of methyl n-propyl ether in milligrams, the final equation becomes:

3. Mg. ether $= (5 - X)\ \frac{(3)(1.67 \times 10^{-5})(7.408 \times 10^{4})}{5}$

4. Thus Mg. ether $= (5 - X)(0.742)$

In the actual determinations on blood samples, a blank was always carried out on the patient's blood before anesthesia, and the amount of $K_2Cr_2O_7$ solution unused by the blank was substituted for the 5 in equation 4. In this way a correction was introduced in case any volatile oxidizable substances were present in the blood of the unanesthetized patient.

In adapting this method for the determination of other ethers, changes would have to be made in this calculation in order to allow for differences in molecular weight and in the degree of oxidation.

EXPERIMENTAL

A. Apparatus: The apparatus used for the determination is shown in figure 1. The $CaCl_2$ tube and H_2SO_4 scrubbing tower A were used to remove moisture and volatile oxidizable substances from the air, which was drawn through the apparatus by means of suction as indicated at the top of column E. The flask C held the sample through which the air current was passed, and the flask D contained the oxidizing medium. The tower E was filled with glass beads into which the oxidizing solution was drawn by the suction. The beads caused the breaking up of the air stream containing the ether vapor into small bubbles, thus insuring thorough contact with the oxidizing solution. Ground glass connections were used throughout except the tube connections indicated on the diagram. These connections were effected by small pieces of transparent Tygon * tubing which were entirely airtight. The 2-way stopcock B allowed the air to be directed either through the sample flask or the bypass.

B. Reagents:

1. 0.100 N $K_2Cr_2O_7$ solution—containing 4.902 g. powdered dried reagent grade $K_2Cr_2O_7$, per liter.
2. 0.01 N $Na_2S_2O_3$ solution—containing about 2.5 g. $Na_2S_2O_3$ and a small amount of Na_2CO_3 per liter. This solution was made and standardized according to the directions of Kolthoff and Sandell (2).
3. 75 per cent by weight solution of H_2SO_4.
4. Reagent grade KI crystals.
5. Starch solutions (3).
6. Reagent grade $BaCl_2.2H_2O$ crystals.

* Will Corporation.

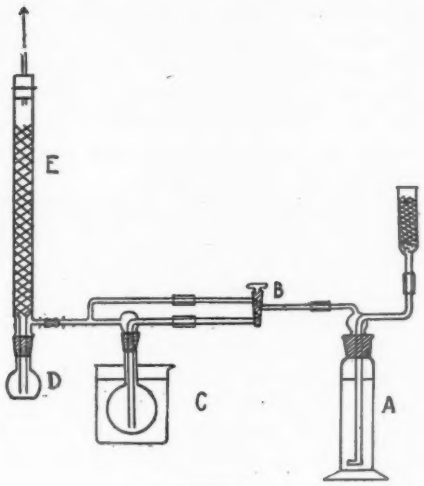


FIGURE 1.

In making these solutions care should be taken that the distilled water is free from oxidizable volatile material. Traces of H_2S found in some water are especially troublesome, and such water must be boiled in the open air in order to expel volatile impurities.

In addition to the foregoing reagents, a standard solution of the ether should be prepared for use in testing the apparatus and acquiring facility with the method. In the case of metopryl, one ml. of the ether at exactly 16 C. drawn into a chilled pipet and added rapidly to 999 ml. of distilled water at the same temperature will give a solution containing 0.726 mg. per ml. This solution should be kept cold and made fresh every two or three days.

C. Drawing the blood: Blood was drawn from the patient by the anesthetist in the operating room. A few crystals of sodium oxalate in the syringe will prevent clotting. A 5 ml. graduated syringe was used and 5 ml. of blood were drawn from the patient before the anesthetic had been administered. A second sample was taken at the point in the anesthesia which was judged clinically to be suitable for surgery (usually second or third plane, third stage). When the blood was drawn, the needle was removed at once and an airtight syringe cap was placed on the syringe. It was then promptly placed in an ice bath or the freezing compartment of an ice box and the blood was not removed from the syringe for analysis until it was thoroughly chilled.

D. Procedure: Exactly 5 ml. of the $K_2Cr_2O_7$ solution and 20 ml. of 75 per cent H_2SO_4 were placed in the reagent flask, heated with a Bunsen burner until boiling began (about 1 minute), and boiled for one half minute. The 2 ml. sample of oxalated blood was measured from the 5 ml. syringe into the chilled sample flask, containing 15 ml. of cold

distilled water, and the flask was immediately connected to the apparatus. With the stopcock turned so that the air stream went through the bypass, gentle suction was applied until the oxidizing solution had been drawn up into the column. The stopcock was then turned, directing the air through the sample. A beaker of water at 70 C. was placed under the sample flask, and the air was allowed to pass through the sample for five minutes.

At the end of this time the air was again directed through the bypass, the suction removed, and the reagent flask was lowered from the apparatus. One hundred ml. of distilled water was poured down the column into the flask in divided portions, and a small amount was run from a pipet over the outside of the tube extending below the glass joint of the column. The flask was then cooled in ice water.

The sample flask was removed and the tube rinsed off with distilled water and dried on the outside. One hundred ml. of 75 per cent sulfuric acid (which may be used repeatedly) was poured down the column of beads in divided portions. The apparatus was then ready for another determination.

The cooled reagent solution was transferred quantitatively into a 500 ml. Erlenmeyer flask using 100 ml. of distilled water in several portions. Approximately 50 g. of $BaCl_2.2H_2O$ crystals was added to the solution, and the flask was shaken until the precipitation of $BaSO_4$ seemed to be complete. About 0.6 g. crystalline KI was then added, and 0.01 N sodium thiosulfate solution was run in from a 50 ml. buret until the brown color of iodine had nearly disappeared. Ten cubic centimeters of starch solution was then added, and the titration continued until the color of the mixture turned from light blue to white.

RESULTS

One example selected from a number of experiments on aqueous solutions of known quantities of ether in blood will suffice to illustrate the results obtained using this method. In this one case the calculation is shown in detail.

Reagent blanks in duplicate showed a loss of 0.46 ml. of 0.100 N $K_2Cr_2O_7$ out of a total of 5 ml. started with, leaving 4.54 ml. on which the calculation is based. The actual volumes of thiosulfate solution required in the titration of the ether samples were 34.2 and 34.4 ml., respectively, at normality 0.0104. Calculating from these titrations the quantities of $K_2Cr_2O_7$ still present in the solution we have 3.56 and 3.58 ml. Subtraction of these from the blank value gave 0.98 and 0.96 ml. of 0.100 N $K_2Cr_2O_7$ solution consumed by the oxidation of the ether. Multiplying each of these values by the calculated factor of 0.742 to determine the milligrams of ether in each case, we have 0.727 and 0.712. The known amount of ether used in each of these determinations was 0.726 mg. A short list of similar results on known quantities of ether is tabulated:

Mg. Ether Used	Analytical Results in Duplicate	
0.726	0.727	0.712
1.550	1.580	1.550
2.180	2.240	2.220

These data indicate that the method affords a satisfactory degree of accuracy.

A tabulation of results obtained on 10 surgical patients selected from a series of clinical cases will show the results obtained on blood.

A complete report on the clinical significance of blood concentrations of the anesthetic will appear in a subsequent publication. The findings on the entire series will be reported at that time. The results included here are intended only as a demonstration of the method in actual practice.

The lack of agreement in a few of the cases listed in the table is ascribed to the difficulty in measuring blood accurately. Syringes with tight fitting plungers and dark lines around the bottom of the plunger afford the highest degree of accuracy.

SUMMARY

A method has been described by which methyl n-propyl ether concentrations in the blood of anesthetized patients may be determined.

The stoichiometric relationships involved in the method have been discussed.

An improvement in the reproducibility of the iodometric titration has been described.

Blood levels of methyl n-propyl ether in 10 surgical patients have been reported.

No.	Blank ($K_2Cr_2O_7$ left)	Titration Ml. of Thiosulfate		Ml. Dichromate Consumed in Reaction		Mg. Per Cent Metopryl		Normality of Thiosulfate
1	4.60	30.5	29.2	1.48	1.42	54.8	52.7	1.040×10^{-2}
2	4.75	35.4	35.5	1.07	1.06	39.7	39.4	1.040×10^{-2}
3	4.70	25.8	20.1	2.02	2.60	75.0	96.5	1.040×10^{-2}
4	4.88	28.1	28.5	1.27	1.22	47.2	45.3	1.286×10^{-2}
5	4.92	29.4	29.4	1.14	1.14	42.3	42.3	1.286×10^{-2}
6	4.85	26.5	22.1	1.44	2.01	53.4	74.5	1.286×10^{-2}
7	4.80	31.3	29.0	0.78	1.07	29.4	39.6	1.286×10^{-2}
8	4.62	23.0	22.4	1.77	1.84	65.7	68.2	1.24×10^{-2}
9	4.54	23.3	23.1	1.65	1.68	61.2	62.2	1.24×10^{-2}
10	4.52	19.0	20.0	2.35	2.48	87.2	75.7	1.24×10^{-2}

REFERENCES

1. Andrews, E.; Potter, R. M.; Friedemann, T. E., and Livingstone, H. M.: Determination of Ethyl Ether in Blood, J. Lab. & Clin. Med. **25**: 966–970 (June) 1940.
2. Kolthoff and Sandell: Textbook of Quantitative Inorganic Analysis, New York, Macmillan, 1936, p. 594.
3. Kolthoff and Sandell: Textbook of Quantitative Inorganic Analysis, New York, Macmillan, 1936, p. 589.

STUDIES ON DIFFUSION RESPIRATION.* II. SURVIVAL OF THE DOG FOLLOWING A PROLONGED PERIOD OF RESPIRATORY ARREST

LAURENCE W. ROTH, PH.D.,† RICHARD W. WHITEHEAD, M.A., M.D. AND WILLIAM B. DRAPER, M.SC., M.D.

Denver, Colorado

Received for publication August 20, 1946

DRAPER and Whitehead (1), in 1944, described a type of respiration (called by them "diffusion" respiration) that, under certain conditions, occurs in dogs in the absence of respiratory movements of the chest. Their experiments showed that dogs held in respiratory arrest by the continuous injection of pentothal sodium continued to obtain sufficient oxygen from the atmosphere to maintain life for periods up to an hour or more provided that (a) the nitrogen of the atmosphere and respiratory tract had been largely replaced with oxygen at the time breathing ceased, (b) the circulation remained adequate and (c) the airway patent. They attributed the maintenance of alveolar oxygen at an adequate concentration during respiratory arrest to suction inward of atmospheric oxygen by the "hemoglobin-oxygen pump." The mechanism of this pump was explained as follows: Oxygenation of the reduced hemoglobin in transit through the respiratory capillaries of the lung lowers the tension of oxygen and total gas pressure within the respiratory spaces. An inward diffusion of the atmosphere results. If the atmosphere so drawn in consists of pure oxygen, the alveolar oxygen tension is maintained by this mechanism at an adequate level for periods of an hour or more of respiratory arrest. It was also demonstrated that, under the appropriate conditions, the "hemoglobin-oxygen pump" can develop a negative pressure of 10 cm. of water or a suction force upon the atmosphere comparable to that developed by a normal inspiration. Draper and Whitehead emphasized that no external force of any kind is applied to the body in diffusion respiration, and that, consequently, the phenomenon is quite distinct from the well known "respiration without respiratory movements" whether produced by streams of air under pressure (2, 3) or by rhythmically induced changes in the barometric pressure of the ambient air (4, 5).

The energy responsible for gas exchange between the atmosphere and the lung alveoli during diffusion respiration is supplied by the

* From the Department of Physiology and Pharmacology, School of Medicine, University of Colorado, Denver, Colorado.

† Present Address, Abbott Laboratories, Chicago, Ill.

body itself. From the point of view, therefore, of the origin of its motivating force, diffusion respiration is a form of natural respiration. It is "artificial" only in the sense that the condition requisite for its appearance, i.e., replacement of nitrogen by oxygen, is not present in nature.

The experiments described by Draper and Whitehead, however, were acute and, consequently, did not provide information with regard to the ability of their animals to survive and ultimately recover from this ordeal. An attempt has been made in the following experiments to deal with this aspect of the problem.

PROCEDURE

The experiments were conducted in Denver where the barometric pressure averages 630 mm. of mercury. Small mongrel dogs were used. Under pentothal sodium anesthesia a sterile injection cannula was tied into one of the cephalic veins. A chest pneumograph was then adjusted and the entire animal placed in a chamber having a capacity of 5,300 cc. and provided with windows allowing continuous observation of the dog. In order to ensure patency of the airway, a mouth gag was used and the tongue kept pulled forward. Throughout the experiment, 12 liters of oxygen per minute were admitted into the chamber. The development of positive pressure within the chamber, however, was prevented by a provision for the free exit of gas. Partial denitrogenation was then accomplished by allowing the animal to breathe pure oxygen for fifteen minutes. Following denitrogenation, respiratory arrest was produced and subsequently maintained for a standard period of forty-five minutes by the continuous infusion of a 1 per cent solution of pentothal sodium, supplied as needed by means of a variable speed mechanical injector.

On completion of the standard forty-five minute period of respiratory arrest, the dog was removed from the chamber and a sample of alveolar gas taken either immediately or after three minutes' exposure to atmospheric air. After the first sample of alveolar gas had been obtained, resuscitation was carried out by means of manual artificial respiration and the administration of oxygen. An additional sample of alveolar gas was secured thirty minutes after the beginning of artificial respiration. On resumption of spontaneous respiration, the dog was given 150 to 200 cc. of 1/6 molar Ringer-lactate solution and 1/2 to 1 Gm. of sodium sulfadiazine intravenously and the foreleg wound was closed aseptically.

EXPERIMENTAL RESULTS

Fifteen such experiments were conducted. The following protocol is representative of the series. This dog (exp. 5) was anesthetized and denitrogenated by the standardized procedure outlined. After

respiratory arrest, an additional dosage of 12.5 cc. of 1 per cent pentothal sodium solution was administered slowly during the next half hour to prevent resumption of spontaneous breathing. The pneumographic record in figure 1 demonstrates that respiratory movements of the chest were absent for forty-five minutes and that spontaneous respiration returned following fifteen minutes of manual artificial respiration. The visible cardiac pulsations remained strong and regular throughout the period of respiratory paralysis. At the beginning of diffusion respiration, the heart rate was 108 per minute. In the following ten minutes, it slowed to 88 but the rate gradually increased thereafter, until, at the end of forty-five minutes of respiratory arrest, it was 102. The color of the tongue and mucous membranes indicated that the blood was thoroughly oxygenated throughout the period of diffusion respiration.

After forty-five minutes of respiratory arrest within the oxygen chamber, the dog was removed and placed in room air. Almost immediately the color of the tongue began to change from bright pink to blue, and, within three minutes, the animal appeared to be near death. A sample of alveolar gas taken after three minutes of exposure to the atmosphere contained 11 per cent oxygen and 39.5 per cent carbon dioxide. Artificial respiration and the administration of oxygen, however, rapidly resuscitated the animal and in fifteen minutes spontaneous respiration began. Thirty minutes later the alevolar carbon dioxide had fallen to 7 per cent and sixty minutes later it had returned to normal. Subsequent treatment consisted of sterile closure of the foreleg wound and the intravenous administration of 200 cc. of 1/6 molar Ringer-lactate solution and 0.8 Gm. of sulfadiazine. The following day the dog had recovered sufficiently to stand. Recovery was uneventful and the dog at the time of writing, sixteen months later, is alive and appears normal.

The essential data from the series are summarized as follows:

(a) *Survival:* Of the 15 dogs in the series, 2 died after forty-three and thirty-five minutes, respectively, of respiratory arrest. The death

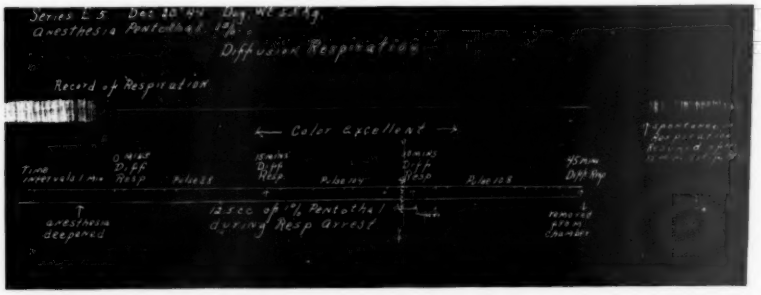


Fig. 1. Kymographic Record of Experiment 5. See protocol, page 295 for details.

of one of these dogs (exp. 7) appears to have been due to an adductor spasm of the cords produced by the anesthetic. The death of the other (exp. 10) was probably the result of an overdose of pentothal sodium. The remaining 13 dogs survived the forty-five minutes of respiratory arrest and were resuscitated by means of artificial respiration and oxygen to the extent that spontaneous breathing was resumed. Four of the 13, however, died within the next forty-four hours. Although the reason for the failure of these 4 dogs to survive permanently was not ascertained with accuracy, it is evident that, in at least 3 of them (see table 1, exp. 1, 9 and 13) the diffusion of atmospheric oxygen to the lung alveoli during the respiratory paralysis was more than adequate. The color of the tongue of the remaining dog (exp. 6) was bright pink at the end of forty-five minutes of respiratory arrest, and, consequently, it appears reasonable to assume that the concentration of alveolar oxygen at the time of its removal from the oxygen chamber was adequate. This particular dog, however, was one of those which were allowed to remain in room air for three minutes before artificial respiration was begun and before an alveolar gas sample was taken. As was the case with the 3 other dogs which we exposed to room air after removal from the oxygen atmosphere, the tongue rapidly became cyanotic and at the end of three minutes, the animal appeared near death. A sample of alveolar gas taken at the end of the three minutes' exposure to room air contained only 4 per cent oxygen. Exposure to room air during respiratory arrest appeared to be especially injurious to this dog and its death may have been the delayed result of the consequent severe anoxemic strain.

(b) *Alveolar Gases:* In six experiments the average alveolar oxygen concentration immediately after completion of forty-five minutes of diffusion respiration but before removal from the oxygen atmosphere was 28.8 per cent. In the case of the 4 dogs exposed for three minutes to room air before a sample of alveolar gas was taken, the average alveolar oxygen was only 9.9 per cent. We attribute the rapid fall in the concentration of alveolar oxygen after exposure to room air to the suction inward of atmospheric nitrogen during respiratory arrest by the "hemoglobin-oxygen pump." The average alveolar concentration of carbon dioxide on completion of the period of respiratory arrest but before removal from the oxygen chamber (eight experiments) was 43.0 per cent, and in the 4 dogs exposed to room air for three minutes it was 43.9 per cent. Exposure to room air, therefore, in contrast to its effect on alveolar oxygen, produced no significant change in the level of the alveolar carbon dioxide. After thirty minutes of respiratory movements of the chest, either spontaneous or artificial, the average level of alveolar carbon dioxide had fallen to 13.3 per cent.

(c) *Rate and Strength of Heart and Color of Tongue:* At the time respiration ceased, the heart rate, as determined from the visible cardiac pulsations, averaged 119 per minute. At the end of the first

TABLE 1

Color of Tongue, Alveolar Gases, Survival, etc., of the Dogs in the Series

Exp. No.	Minutes of Diff. Resp. Completed	Color of Tongue on Removal from Oxygen Chamber	Minutes of Artif. Resp. Required for Resuscitation	Alveolar Gases on Completion of Diff. Resp.				Survival after Experiment	Comments
				(a) Immediately after removal from oxygen chamber		(b) After three minutes of exposure in respiratory arrest to room air			
				O_2, %	CO_2, %	O_2, %	CO_2, %		
1	45	Mod. Cyanosis	11	32.2	40.0	—	—	2½ hrs.	Death precipitated by aspiration of vomitus
2	45	Sl. Cyanosis	2½	—	44.0	—	—	42 days	Died of distemper
3	45	Excellent	5	—	38.0	—	—	6 mos. +	
9	45	Excellent	5	24.0	39.0	—	—	44 hrs.	Necropsy showed areas of atelectasis
11	45	Mod. Cyanosis	3	33.3	43.7	—	—	6 mos. +	
12	45	Sl. Cyanosis	7	Invalid	Sample	—	—	6 mos. +	
13	45	Excellent	57	30.5	43.5	—	—	5½ hrs.	Unusually large dose of anesthetic. Probably anesthetic death. Note long period required for resuscitation
14	45	Excellent	3½	29.5	44.0	—	—	6 mos. +	
15	45	Sl. Cyanosis	17½	23.0	52.0	—	—	6 mos. +	
4	45	Excellent	24	—	—	16.0	38.0	62 days	Died of leptospirosis
5	45	Excellent	15	—	—	11.0	39.5	6 mos. +	
6	45	Excellent	5	—	—	4.0	45.0	17 hrs.	Death probably owing to acute anoxia precipitated by exposure in respiratory arrest to room air
8	45	Excellent	4½	—	—	8.5	53.0	75 days	Cause of death unknown
7	43	—	—	8.5	52.5	—	—	—	Cords strongly adducted. Death due to obstruction Note low alv. O_2 and high CO_2
10	35	—	—	—	—	—	—	—	Probable anesthetic death

ten minutes of respiratory arrest the average heart rate had fallen to 114. Subsequently it rose slowly to reach 127 per minute at the conclusion of the period of diffusion respiration. In the majority of the dogs, the visible cardiac beat appeared to get stronger during the first twenty minutes of respiratory arrest, but in the last fifteen minutes there was a tendency for it to weaken. In every experiment the color of the tongue remained bright pink during the first half hour of respiratory arrest. Cyanosis, when encountered, appeared only in the last fifteen minutes. Thus, from the behavior of the animals in our series, it appears that thirty minutes of diffusion respiration is relatively safe in dogs, but that beyond this period deterioration of the circulation and consequently of the oxygen saturation of the blood may be anticipated.

(d) *Rectal Temperature:* During the forty-five minutes of diffusion respiration and while the dogs were still within the gas-tight chamber, the average fall in temperature was only from 101 F. to 100.9 F. Following removal of the animal from the chamber and with the beginning of respiratory movements of the chest the temperature fell

more rapidly. At the end of thirty minutes of respiration, either spontaneous or artificial, the average temperature was 99.0 F. After sixty minutes of respiration, it had fallen to 96.4 F. It will be noted that the fall in rectal temperature coincided with the reestablishment of breathing and with the fall in the level of alveolar carbon dioxide.

(e) *Recovery:* Recovery from the anesthesia and other effects of the experiment was slow but within forty-eight hours all of the surviving dogs were able to stand and at the end of a week had almost entirely recovered.

(f) *After-Effects:* No disturbance in behavior, appearance, appetite, or weight was detected in the 9 dogs that made a permanent recovery.

COMMENT

The data presented in this paper show that, with the aid of diffusion respiration, a substantial proportion of dogs are capable of making complete and permanent recovery from a procedure which imposes the following stresses: (a) complete abolition of respiratory movements of the chest for forty-five minutes, (b) an otherwise fatal level of pentothal sodium anesthesia maintained during forty-five minutes of respiratory arrest, and (c) the slow accumulation of alveolar carbon dioxide during the respiratory arrest to a peak, in one case, of 53 per cent.

The survival of the dogs undoubtedly was owing to the fact that an adequate concentration of alveolar oxygen was maintained throughout the period of respiratory arrest, through the action, we believe, of the "hemoglobin-oxygen pump." The delay in the onset of anoxemia as long as the nonbreathing dog is kept in an atmosphere of oxygen is in marked contrast with its rapid onset in room air and lends support to our contention that, as long as there is circulation, the atmosphere continues to be drawn into the lungs after breathing has ceased.

Experienced anesthetists will realize that these experiments involved a difficult problem in anesthesia. A level of anesthesia profound enough to prevent spontaneous breathing had to be maintained for forty-five minutes without serious injury to the circulation. The difficulties encountered were increased by the absence of guiding signs in this level of anesthesia and there is no doubt that on many occasions the anesthesia was more profound than the minimum required to maintain respiratory arrest. In spite of this handicap, 13 of the 15 dogs survived the period of respiratory arrest and subsequently resumed spontaneous breathing. It seems fair to conclude from this that a wide margin exists in pentothal sodium anesthesia between respiratory arrest and failure of the circulation provided the alveolar oxygen is maintained at a high level.

The fact that the alveolar carbon dioxide had risen to an average level of 43 per cent at the end of respiratory arrest demonstrates that

the outward diffusion of carbon dioxide is much slower than the inward diffusion of oxygen. Even if carbon dioxide were nontoxic, therefore, its accumulation during diffusion respiration would eventually cause death through the exclusion of oxygen from the respiratory spaces. This difference between the behavior of oxygen and carbon dioxide is probably explained by the fact that, in contrast to the inward diffusion of oxygen, the outward diffusion of carbon dioxide is not aided by a mechanism analogous to the "hemoglobin-oxygen pump." According to Leake and Waters (6), concentrations of carbon dioxide above 40 per cent are definitely depressant to both the respiration and circulation of dogs. In our experiments, the dogs were most likely to begin breathing spontaneously, i.e., to break through the depressant effects of the anesthetic at about the twentieth minute of respiratory arrest. Deterioration of the circulation and anoxemia were not observed until after thirty minutes of arrest, i.e., at the time which coincided with the accumulation of alveolar carbon dioxide to a high level. Our experiments were not designed to measure the synergistic effects of carbon dioxide on pentothal sodium anesthesia, but it was, nevertheless, noticeable that the dogs required very little additional anesthetic after the first thirty minutes of respiratory arrest, and that the sleeping time following resuscitation was quite prolonged—lasting in some experiments for more than twenty-four hours. This latter observation is in agreement with the findings of Barbour and Seevers (7) that the sleeping time of rats anesthetized with pentobarbital is prolonged in atmospheres containing 10 or 20 per cent carbon dioxide.

In a recent review Comroe and Dripps (8) have suggested that vigorous cardiac contractions, diaphragmatic flutter, ciliary action and the movement of gas set up when carbon dioxide is absorbed by soda lime may be either alternative or supplementary mechanisms for the "hemoglobin-oxygen pump" postulated by Draper and Whitehead (1). It is well known that the cardiac contractions generate small back-and-forth oscillations of the gas within the respiratory passages, but it is difficult to conceive that the high concentrations of alveolar oxygen we have found could have been maintained by this mechanism. In any case, the small, intermittent to-and-fro puffs generated by cardiac contractions could not produce the progressive and uninterrupted development of 10 cm. of water of negative intrapulmonic pressure shown in figure 2 of (1). Much the same may be said of diaphragmatic flutter. It is, of course, possible that ciliary action may produce a slight motion of the gas within the respiratory tract but, here again, the resulting gas exchange could only be insignificant and would almost certainly be inadequate to sustain life during an hour of respiratory arrest. Comroe and Dripps have cited the work of Hilding (9) in support of this latter suggestion. The latter author has shown that the outward movement of a succession of occluding mucous plugs along the trachea under the influence of the cilia can lead to the development

of as much as 4 cm. of water of negative intrapulmonic pressure *behind* the moving plugs. Such a mechanism may explain, in part, the slow development of atelectasis but can hardly be responsible, as suggested by Comroe and Dripps, for the phenomenon of diffusion respiration. Inasmuch as the mechanism described by Hilding depends upon the existence of plugs which occlude the respiratory passages and which consequently *prevent* the atmosphere from gaining entrance into the respiratory spaces, it is evident that this mechanism would oppose rather than facilitate diffusion respiration. Currents of gas set up by the absorption of carbon dioxide by soda lime might conceivably have aided in the ventilation of the alveoli in those experiments in which a spirometer equipped with a soda lime chamber was used (1) but the fact that diffusion respiration is efficient in an oxygen chamber in which no soda lime is used shows that any movement of gas generated in this way is unimportant.

In another review article (10) Comroe and Dripps stated that Draper and Whitehead (1) and Roth, Whitehead and Draper (11) have confirmed the finding of Meltzer and Auer (3) to the effect that the intratracheal insufflation of oxygen will maintain life for hours in the absence of respiratory movements of the chest. This is an error. Intratracheal insufflation of oxygen is not employed in diffusion respiration nor, in fact, is any other form of external energy applied.

SUMMARY

1. Fifteen dogs were placed in an oxygen chamber and, after partial denitrogenation, were held in respiratory arrest by the continuous administration of pentothal sodium for a standard period of forty-five minutes.

2. Two dogs died after thirty-five and forty-three minutes, respectively, of respiratory arrest. The remaining 13 dogs were alive at the end of forty-five minutes of respiratory arrest and were resuscitated to the extent that they resumed spontaneous respiration.

3. Of the 13 surviving dogs, 4 died from various causes in the following forty-four hours. The remaining 9 made a complete and permanent recovery.

4. At the end of forty-five minutes of respiratory arrest, the average concentration of alveolar carbon dioxide in 8 dogs was 43.0 per cent. After thirty minutes of respiratory movements of the chest, this had fallen to 13.3 per cent. The average concentration of alveolar oxygen at the end of forty-five minutes of respiratory arrest, but before removal from the oxygen atmosphere, was 28.8 per cent in 6 dogs. In 4 dogs exposed to room air for three minutes after their removal from the oxygen chamber, the average alveolar oxygen was only 9.9 per cent.

5. We attribute the survival of these dogs and the maintenance of

their alveolar oxygen at a high level during prolonged respiratory arrest to the existence of diffusion respiration.

A generous supply of pentothal sodium was furnished through the courtesy of the Abbott Laboratories, Chicago.

REFERENCES

1. Draper, W. B., and Whitehead, R. W.: Diffusion Respiration in the Dog Anesthetized by Pentothal Sodium, Anesthesiology 5: 262–273 (May) 1944.
2. Hooke, R.: An Account of an Experiment Made by M. Hooke, of Preserving Animals Alive by Blowing Through Their Lungs With Bellows, Phil. Trans. Roy. Soc. 2: 539–540, 1667.
3. Meltzer, S. J., and Auer, J.: Continuous Respiration Without Respiratory Movements, J. Exper. Med. 11: 622–625 (July) 1909.
4. Thunberg, T.: The Barospirator: A New Machine for Producing Artificial Respiration, Skandinav. Arch. f. Physiol. 48: 80–94, 1926.
5. Barach, A. L.: Immobilization of Lungs Through Pressure, Am. Rev. Tuber. 42: 586–613 (Nov.) 1940.
6. Leake, C. D., and Waters, R. M.: The Anesthetic Properties of Carbon Dioxide, Anesth. & Analg. 8: 17–19 (Jan.–Feb.) 1929.
7. Barbour, J. H., and Seevers, M. H.: A Comparison of the Acute and Chronic Toxicity of Carbon Dioxide With Especial Reference to its Narcotic Action, J. Pharmacol. & Exper. Therap. 78: 11–21 (May) 1943.
8. Comroe, J. H., Jr., and Dripps, R. D., Jr.: Applied Physiology, Ann. Rev. Physiol. 7: 653–676, 1945.
9. Hilding, A. C.: Production of Negative Pressure in the Respiratory Tract by Ciliary Action and its Relation to Postoperative Atelectasis, Anesthesiology 5: 225–236 (May) 1944.
10. Comroe, J. H., Jr., and Dripps, R. D.: Artificial Respiration, J. A. M. A. 130: 381–383 (Feb. 16) 1946.
11. Roth, L. W.; Whitehead, R. W., and Draper, W. B.: Studies on Diffusion Respiration: II. Recovery Following Prolonged Respiratory Arrest, Federation Proceedings 4: 61 (Mar.) 1945.

PROGRAM OF MEETING OF THE SECTION ON ANESTHESIOLOGY OF THE MASSACHUSETTS MEDICAL SOCIETY

Hotel Statler, Boston, Mass.

May 20–22, 1947

"The Role of Anesthesia in the Treatment of Bronchiectasis," by Lloyd H. Mousel, M.D., Co-director of Department of Anesthesia, George Washington Medical School, Washington, D. C.

"The Use of Anesthetic Drugs in Medical Practice," by Dr. Perry P. Volpitto, M.D., Director of Department of Anesthesiology, University of Georgia Medical School.

"Standardization of Economics of Anesthesia," by Perry P. Volpitto, M.D.

THE PITTSBURGH SOCIETY OF ANESTHESIOLOGISTS will meet at the Pittsburgh Academy of Medicine on June 26, 1947. The program will consist of case presentations for discussion by the Anesthesia Study Committee, headed by Dr. Eldon B. Tucker, Chairman.

PROBLEMS IN SUPPLY OF ANESTHETIC GASES IN THE EUROPEAN THEATER OF OPERATIONS, U. S. ARMY *

COLONEL RALPH M. TOVELL †

Medical Corps, Army of the United States

Submitted for publication August 29, 1946

IT was with some hesitation and diffidence that I accepted an invitation to present a paper before this gathering, which is representative of the Compressed Gas Industry. I do not claim to be a business man interested in the supply of gases except as a doctor is interested in the supply and identification of the medicinal agents that he uses. I was thrust into a position which, for me, was unique when I was recruited and sent overseas to become Senior Consultant in Anesthesiology to the Chief Surgeon of the European Theater of Operations, U. S. Army. I thought that you would be interested in hearing of the difficulties which anesthetists encountered in that effort which, as you know, was a major one of tremendous proportions. It is my intention to outline to you in chronologic order situations in reference to supply of anesthetic gases which were encountered. In order to facilitate that outline, it is best to describe certain factors in organization.

Immediately upon arrival of the Senior Consultant in Anesthesiology in England, in September 1942, at the Headquarters of the Service of Supply, he became a member of the Professional Service Division in the Office of the Chief Surgeon and, in that capacity, he represented anesthetists. His associates were specialists, each representing his particular specialty. The Division was directed by Colonel James C. Kimbrough, M.C., and it was divided into two Sections; one surgical under the leadership of Colonel Elliott C. Cutler, M.C.; and the other medical under the guidance of Colonel William S. Middleton, M.C. Because anesthetists render their service to patients at the same time as surgeons, anesthesiology was considered as a subdivision of the Surgical Section but because anesthesiology involves so many considerations that are medical in scope, liaison with the Medical Section was close. The function of personnel of the Division was to observe, report and recommend, through the Director, to the Chief Surgeon. Observation included all phases of unit organization, supply of equipment and therapeutic agents, as well as an evaluation of personnel in reference to prac-

* Presented at the Annual Meeting of the Compressed Gas Manufacturing Association, New York City, 29 January 1946.

† Chief, Department of Anesthesiology, Hartford Hospital, Hartford, Conn.

tice. In the early stages of planning for invasion of northwestern Europe, Tables of Supply were studied for each type of unit in relation to the task that it was designed to fulfill. Items of equipment and supply were deleted, others were added, to meet the needs of current practice.

In order to carry out these duties intelligently, it was considered that the first requisite was to become familiar with provisions for anesthesiology in the British and Canadian Armies. Following renewal of acquaintance with Air Commodore R. Macintosh, Senior Advisor in Anesthetics to the Royal Air Force, and with Colonel Beverly Leach, C. O. 5th Canadian General Hospital, arrangements were made to meet Lieutenant Colonel Ashly Daly, Senior Advisor in Anesthetics to the British Army. These men offered the fullest cooperation in making arrangements for me to visit and interview anesthetists in British and Canadian hospitals. Inspection of several British hospitals, both military and in the Emergency Medical Service (civilian), revealed that they were equipped to carry on all phases of anesthesia such as would be conducted in their normal civilian hospitals, with the exception that in military hospitals provision was not made for the use of cyclopropane and carbon dioxide absorption. Anesthetic machines were procured from several British companies. Expendable items and parts were not completely standardized and, therefore, were not completely interchangeable. Inspection of Canadian hospitals revealed that equipment of American origin equaled that in civilian hospitals in the United States or Canada. Anesthetic machines were standardized, all being of the same model, providing for the use of carbon dioxide absorption and cyclopropane. Anesthetic gases were supplied in cylinders of Canadian origin in design and manufacture.

It was found that American military hospitals, in late 1942, were equipped partially with anesthetic machines of British origin requiring the employment of cylinders of British design and manufacture. Refilling of cylinders was accomplished through British trade channels. New hospitals arriving from the United States brought anesthetic machines of American manufacture, produced by two well-known companies. Expendable items and parts were not interchangeable in the relation of one American machine to the other, nor in relation to the British machines already possessed in other hospitals. Because expendable parts were not interchangeable, four pools of maintenance items were established by the Supply Division in order to fill requisitions for parts for anesthetic machines built by two British Companies, the British Oxygen Company and the Medical and Industrial Equipment Company, and by two American Companies, the Heidbrink Company and McKesson Technical Appliance Company. Descriptions in American Tables of Supply were inadequate to eliminate the possibility of obtaining parts built by one manufacturer when requisitions were submitted for parts for machines built by the other American manufacturer. These difficulties were further enhanced by discrepan-

cies in description and grouping of parts in British and American Supply Tables. Supply officers found it difficult to catalogue and store parts, and issue was complicated because newly arriving anesthetists were unfamiliar with terminology to be employed in making requisitions. These conditions in supply influenced practice and during an emergency in an operating room, unless the anesthetist was ingenious and had thoroughly prepared for it, the outcome of a critical operation was put in jeopardy. When a sudden need for accessory equipment arose, nurses and corpsmen were likely to respond to it by bringing parts that would not fit.

Cylinder yokes of American machines were of typically American design and were not of the design usually supplied by American manufacturers for export to Great Britain which would accommodate either American cylinders or British cylinders number seven. Lack of standardization made it necessary for the U. S. Army to procure and distribute cylinders of both British and American origin. Shipping space was at a premium and because of this, it was necessary to equip American gas machines with British cylinders. This could be done only after the procurement of suitable adapters for reducing regulators for oxygen and for nitrous oxide, in the case of all cylinders of over 450 gallons capacity. Yoke adapters were procured for American cylinders, designated sizes C and D. The medical section of the British Oxygen Company, under the direction of Mr. H. A. Chapman, was very helpful in evolving designs of these adapters and in the production of models. Requisitions for some thousands of the several adapters were processed through to American Headquarters to the British Ministry of Supply. Procurement through British channels necessitated allocation of scarce metals, manufacturing facilities, and labor to produce them. All this was time-consuming and delivery was slow in spite of the fact that duplicating requisitions were placed in the United States. British suppliers were forced to equip their filling stations with adapters to accommodate American cylinders and to orient their workmen in recognition of American cylinders and identification of the gas required for each type. It was necessary to take precautions that American cylinders filled through British trade channels were delivered only to American hospitals possessing American anesthetic equipment, while British cylinders were delivered to hospitals possessing only British equipment. As can be easily realized, such diversion in channels of supply is difficult and particularly so in a Theater of Operations suffering from "growing-pains."

These major difficulties of supply were enhanced by the practice in the United States of shipping a gas machine in one crate and equipment of deteriorating quality (rubber parts) in another. This practice was predicated on the assumption that, if deteriorating parts were kept in storage with nonexpendable equipment for an appreciable length of time, upon the arrival of such equipment in a Theater of Operations,

they would no longer be usable. The plan had been to "marry" units of expendable equipment with each unit of nonexpendable equipment, at the Port of Embarkation. When this "marriage" failed to take place, machines arriving without their deteriorating parts were useless until deteriorating parts of British design and manufacture could be obtained. This situation was particularly difficult in relation to American machines that were shipped with hospital units intended for use in the North African Theater. As you will recall, the North African Campaign opened on November 8, 1942. Hospital units staged for a very short period in Great Britain, during which time there was no opportunity for anesthetists to check their equipment for completeness before re-embarking for Africa, where procurement of deteriorating parts was impossible because of lack of an established industry as in England where substitute expendable items could be obtained. It was necessary to await arrival of expendable items from the United States. During the early stages of the ship-to-shore operation and thereafter, in many instances, choice of anesthesia was limited to pentothal sodium administered intravenously and to ether administered by the open drop method. Intermittent positive pressure was not available for penetrating wounds of the chest. Fortunately, this situation was corrected at the source and American manufacturers were instructed to deliver each gas machine complete in a single crate.

Early in December 1942, recommendations were submitted through channels to the Surgeon General that: (1) a competent consultant in anesthesiology be obtained to function in Washington in cooperation with Personnel and Supply Divisions; (2) Tables of Supply be amplified to meet modern requirements; (3) standardization of suitable equipment for each type of unit (example: Surgical, Evacuation, Station and General Hospitals) be achieved, permitting interchangeability of rubber parts, endotracheal equipment, and masks; (4) the work of the Committee on Standardization, initiated through the efforts of the American Society of Anesthetists, Inc., be supported and with the cooperation of the Army and Navy, its functions be pushed to their logical conclusions; and (5) this effort, directed toward uniformity of threadings, tapers, outlets, and valves, be coordinated with projects in the Air Force for standardization of methods of supply, storage, and administration of oxygen to air crews.

In 1943, problems in equipment and supply inherent in their design were met by palliative measures. An article entitled, "Consolidated Report Regarding Equipment for Anesthesia and Oxygen Therapy in E.T.O. (Northern Ireland Base Section excepted)," was prepared for submission 31 January 1943. The salient points in the report covered the requirements for gas machines and provision of adapters to permit use of supplies of gases from British sources. It recommended that each hospital be provided with sufficient quick coupling oxygen sets (source, British Oxygen Company) for distribution of oxygen in hos-

pitals to cover the contingency of gas attack. It was pointed out that the use of oxygen tents was impractical in the Theater because of lack of freely available ice and because of difficulties of nursing in cases of multiple wounds. The acceptance by the Senior Consultant in Anesthesiology of responsibility for equipment for oxygen therapy brought to light new difficulties in standardization. Reducing regulators on anesthetic equipment were designed for the use of so-called medical cylinders containing oxygen, the outlets of which had an outside diameter of 0.825 inch. American regulators for oxygen therapy were produced by some American manufacturers designed to utilize commercial cylinders containing oxygen, the outlets of which were 0.903 inch in outside diameter. Other American manufacturers supplied regulators for oxygen therapy designed to fit medical oxygen cylinders. The presence in the theater of two types of American equipment necessitated duplication of means for adaption of British cylinders to each type and also necessitated the procurement of adapters which would permit the utilization of American medical or American commercial cylinders to either American medical or American commercial reducing regulators. The original estimate of the number of adapters required was predicated on the basis that the major supply of anesthetic machines and apparatus for oxygen therapy would be procured from British sources and would, therefore, not need adaption to British cylinders. At the time (31 January 1943), the outcome of the U-boat campaign looked grim but, with the marked Allied successes in dealing with submarines, delivery of equipment from the United States increased beyond original hopes. American machines to which American anesthetists were accustomed arrived in greater numbers than had originally been expected but the procurement of adapters permitting use of British cylinders on them lagged behind needs thus created. It was noted that newly arriving American anesthetists familiar only with American equipment and supplies were at a loss to recognize the uses of adapters that were supplied them in preparation for employment of British cylinders. While they continued to employ American cylinders that had been a part of their unit equipment, adapters that were subsequently needed tended to be misplaced or lost. It was necessary to issue circular letters describing eccentricity in design between American equipment and British supplies, with explanations including diagrams of the use for which the adapters were intended.

In view of this confusion, it is little wonder that an accidental death occurred when an anesthetist, having worked in an American hospital equipped with American supplies, was eventually moved to an American hospital supplied with both British and American cylinders. When an American cylinder was emptied, it was replaced by a British cylinder through the use of one of the adapters supplied. Both cylinders were painted green and, because of lack of easily recognizable means for further identification, he thought that he was dealing with a cylin-

der containing oxygen. Green British cylinders contained carbon dioxide and the patient died because of its administration. This occurrence brought to the fore the problems of identification by color schemes which were national rather than international in scope. As a matter of fact, no national scheme for color identification was fully accepted in the United States. The U. S. Navy had long been using one scheme, whereas civilian hospitals in the United States were supplied with cylinders, approximately 4½ inches in diameter by 26 inches long and smaller, identified by color markings established in Simplified Practice Recommendation R–176–41 approved 29 January 1941. So far as the European Theater of Operations was concerned, identification, in the main, followed this Simplified Practice Recommendation. Unfortunately, in many instances, this scheme of color identification conflicted with the British scheme and grave sources for error were existent both in relation to workmen identifying and refilling cylinders and to anesthetists employing the contents therefrom.

In 1944, a command decision was reached that all American cylinders employed in Great Britain would be repainted according to the British standard color scheme. This entailed a great deal of work, the accomplishment of which in the Medical Department required designation of teams of anesthetists to inspect American depots, identify cylinders as to their contents and supervise their repainting and marking by means of stencils. Between thirteen to fifteen thousand cylinders were thus processed. The effort had been precipitated by delivery to a United States depot of over one hundred cylinders incorrectly filled with carbon dioxide instead of oxygen. Fortunately, only six cylinders had been issued before the error was detected. Upon the recommendation of the Senior Consultant in Anesthesiology, all issuing depots were closed except to meet specific emergencies until the six cylinders were found. They were traced by means of the records, located and emptied without any patient having suffered because no gas had been administered from these cylinders. The project of repainting and stenciling cylinders was undertaken reluctantly because it contravened the principle that only the supplier of gases should identify them and, thereafter, identification should not be altered or added to. The need for adhering to this principle was demonstrated when it was subsequently found by the British Oxygen Company that two cylinders had been marked in error. These cylinders having been so marked when empty, the error in identification was noted when they were to be refilled and so again, no injury to patients resulted. Because of these circumstances, basic contracts negotiated through the British Ministry of Supply were altered and suppliers were made fully responsible for complete identification of gases in cylinders and maintenance of these means of identification including painting and stenciling. This represented a distinct step forward. Difficulties in identification of gases in American cylinders were reported to the Office of the Surgeon General

and subsequently a report was received that the Port of Embarkation had been made responsible for the stenciling of all cylinders to be sent to the European Theater. With the receipt of this report, it was felt that another real step forward had been taken in eliminating hazards of identification. As will be explained, elation over this progressive step was short lived.

In July 1944, an administrative memorandum was issued by the Office of the Chief Surgeon which contained five sections covering the procurement of medical gases, adapters, employment of carbon dioxide mixtures, cyclopropane, and identification of medicinal gases. Although the attachment of cylinders containing pure carbon dioxide to apparatus designed for inhalation therapy or for production of anesthesia had previously been prohibited, this new memorandum publicized the fact that no longer would mixtures of carbon dioxide be available for issue. Elimination of these mixtures was considered the lesser of two evils where difficulty in identification was weighed against questionable clinical advantages accruing from use of the mixtures.

In planning for D. Day, it was established as a general principle that only American-made cylinders would be used in continental operations and British-made cylinders would be used in fixed medical installations in the United Kingdom. Accumulation of American-made cylinders in U. S. Medical Depots was gradually achieved. This was accomplished when empty American-made cylinders were sent in for refill. British-made cylinders were returned to American Hospitals to replace the American-made cylinders that were being segregated for ultimate shipment to France.

The problem of identification of cylinders arose once again after the capture of Paris, France, when the possibility of having French commercial producers refill American cylinders was considered. It was recommended that basic contracts with the French include the stipulation that all cylinders be stenciled in English with the name of the gas contained.

To the dismay of those vitally concerned in the European Theater, late in 1944, cylinders painted lusterless olive drab were received from the United States. It was subsequently learned that in September, a technical bulletin had been issued by the Corps of Engineers in Washington instructing that all cylinders in the future would be painted olive drab, irrespective of the gases contained. It was unforunate that these cylinders did not possess permanent imprints indicating the name of the gas contained but were only stenciled. These stencils were subject to erasure during transportation and in open storage. Such cylinders continued to be received throughout the remainder of the campaign.

Difficulty resulting from the design of cylinders and lack of standardized means of identification of gases contained was not limited to the European Theater of Operations. It was common to all theaters in

matters of principle, differing only in its aspects according to nations and services involved. These difficulties were in part recognized by the combined Production and Resources Board and, as a result, in 1943 a conference was held in the United States followed by another conference in London in August and September 1944. A third conference was held in Ottawa, Canada, in September 1945, including representatives from the United Kingdom, Canada and the United States. The London conference was for the purpose of receiving information of British and American standards in order that adapters might be designed and produced. Difficulties arose in the production of adapters owing to multiple standards in the United States and the third conference was to coordinate latest information on acceptable American standards. Emphasis was placed on acceptance of standards that provided for noninterchangeability of gas connections, thus safeguarding against linkages that might be made in error. The report of the Compressed Gas Manufacturers Association entitled, "American Compressed Gas Cylinder Valve Outlets," lists three gases, carbon dioxide, nitrous oxide, and oxygen, as being distributed in large cylinders having the same valve outlet. It is highly desirable that this alternate medical standard for oxygen be eliminated completely. Specifications for procurement of valves for the U. S. Army no longer include the medical standards (OD.825). It is hoped that this alternate standard will be eliminated from civilian channels of distribution too. Further remedy can be achieved by discontinuance of the use of carbon dioxide and carbon dioxide and oxygen mixtures for inhalation, leaving only nitrous oxide to be distributed through medical standard valves. The report listed six valves for small cylinders containing medicinal gases, including oxygen, which are equipped with flush outlets. In the case of all these gases, cylinders can be linked in error and no safeguard is provided. It is highly desirable that a project for development of design and establishment of noninterchangeable standards be undertaken. The cooperation of the Compressed Gas Manufacturers Association is solicited. Because the Medical Section of the British Industry is voluntarily undertaking to redesign valves and valve connections for medical gases at this time, if international standardization is to be achieved, the project of establishing noninterchangeability in linkages should be undertaken on an international cooperative basis. In view of the difficulties that were occasioned in the European Theater, including wastage of scarce metal and personnel to fashion adapters, it is sincerely hoped that this will be done in such a manner that alteration of the existing American equipment may be effected as a field fix. In this regard, Dr. Joseph Kreiselman, Civilian Consultant to the Office of the Surgeon General, U. S. Army, following the ideas of Dr. J. A. Heidbrink, has recently developed apparatus for a field fix which will provide noninterchangeability of flush outlets for yokes. It is worthy of serious consideration.

It is with great satisfaction that I can report adoption by the U. S. Army, Navy, and Air Force of a color code for identification of compressed gases in cylinders. It is worthy of acceptance by the Compressed Gas Manufacturers Association and other federal services such as the Bureau of Standards and by the American Standards Association.

In conclusion, difficulties encountered in distribution of compressed gases in the European Theater of Operations, U. S. Army, have been outlined in so far as they affected the practice of anesthesiology. It is obvious that remedial measures of a fundamental nature should be undertaken if lives of the sick and wounded are to be saved.

MEETING OF THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

REGIONAL MEETING IN CONJUNCTION WITH THE

CHICAGO SOCIETY OF ANESTHESIOLOGISTS

Chicago, Ill., May 29 and May 30, 1947

I. Clinical Demonstrations. Thursday, May 29.

Illinois Research Hospital—Dr. W. H. Cassels and associates.
Wesley Memorial Hospital—Dr. Mary Karp and associates.
St. Luke's Hospital—Dr. W. A. Conroy and associates.
Michael Reese Hospital—Dr. B. Stodsky and associates.
University of Chicago Clinics—Dr. H. Livingstone and associates.
Evanston Hospital—Dr. E. Remlinger and associates.

II. Conferences. Friday, May 30 (Memorial Day). Congress Hotel. Afternoon, commencing at 1:30 P.M. E. B. Tuohy, M.D., President A.S.A., presiding.

1. Methods of Testing Analgesics—Carl Pfeiffer, M.D., Chicago, Ill.
2. Intradural Vasoconstrictors—Mary Karp, M.D., Chicago, Ill.
3. Chicago Keysort Anesthesia Record—W. A. Conroy, M.D.; W. H. Cassels, M.D., and Bernard Stodsky, M.D., Chicago, Ill.
4. Chloroform, Old—Donald Kindschi, M.D., Madison, Wis.
   Chloroform, New—Lucien Morris, M.D., Madison, Wis.

III. Dinner—Round Tables with Moderators—Congress Hotel, 6:00 P.M.

IV. Evening Meeting—Congress Hotel, 8:30 P.M., W. A. Conroy, M.D., President C.S.A., presiding.

Symposium on Nitrous Oxide.

1. Some Aspects of Nitrous Oxide-Oxygen Anesthesia—F. W. Clement, M.D., Toledo, Ohio.
2. Oxygen Requirements—W. O. McQuiston, M.D., Peoria, Ill.
3. Combinations of Anesthetic Agents and Procedures—E. B. Tuohy, M.D., Rochester, Minn.

EDITORIAL

SEMANTICS AND ANESTHESIOLOGY

Physicians contemplating a career in anesthesiology are frequently plagued by well-meaning friends who are motivated by a traditional Aristotelian philosophy into admonishing against or, at least, into seriously questioning the expediency of entering a specialty of medicine the work of which has been customarily relegated to technicians. Even without benefit of such deterring counsel, the neo-anesthesiologist, who has been conditioned since birth in an environment which reveres established practice, has difficulty in resolving for himself the numerous conflicts between the dominant orthodox concepts of the prescientific culture and the newer (and more promising) orientations of the age of science.

The deep-seated philosophical convictions which underlie and provoke the expressions of well-meaning friends are not difficult to understand. Nor is it difficult to appreciate the struggle of the embryonic anesthesiologist to free himself from this ancient traditional pattern. In his recent book, People in Quandaries (New York, Harper and Brothers, 1946), Wendell Johnson gives concise expression to the matter.

"Change has been suspect and has been resisted throughout the history of the race. It has been customary for fathers to pass on to their sons the creeds and customs which their own fathers had passed on to them. Ancestors have been worshiped and the Old Man has been honored from time immemorial. Education has been chiefly a matter of compelling the child to conform to the ways of his elders. The student has been taught answers, not questions. At least, when questions have been taught, the answers have been given in the back of the book. In the main, knowledge has been given the student, but not a method for adding to it or revising it—except the method of authority, of going to the book, of asking the Old Man. The chief aim of education has been to make the child another Old Man, to pour the new wines of possibility into the old bottles of tradition."

The physician entering the practice of anesthesiology must be prepared to break with tradition. In freeing himself of this bondage, he demonstrates that he is by nature a man capable of perceiving new horizons, of distinguishing differences as well as similarities, or recognizing that there are questions without immediate answers and of encouraging change. The specialty of anesthesiology enjoys a unique distinction in being peopled with men of this character. The specialty has, by the same token, an obligation to its constituents—an obligation that there be no repression of these men who have helped to perforate the dikes of Aristotelian medical philosophy and that there be continuation of emancipation of medical thinking.

CURRENT COMMENT AND CASE REPORTS

CURRENT COMMENT is a section in ANESTHESIOLOGY in which will appear invited and unsolicited professional and scientific correspondence, abbreviated reports of interesting cases, material of interest to anesthesiologists reprinted from varied sources, brief descriptions of apparatus and appliances, technical suggestions, and short citations of experiences with drugs and methods in anesthesiology. Contributions are urgently solicited. Editorial discretion is reserved in selecting and preparing those published. The author's name or initials will appear with all items included.

PROBABLE IDIOSYNCRASY TO ETHER: A CASE REPORT

The reactions reported below are thought to represent an idiosyncrasy to diethyl ether. In some ways they might be looked upon as an overdose, but did not seem so to the administrator. After successfully giving other agents in a second administration, a change to a small amount of ether was again abruptly followed by the reaction to be described.

L. H., a 16 year old girl, was sole survivor of an auto crash six weeks before admission to this hospital. She received a laceration above the right eye, third degree burns of both lower legs, and was unconscious for thirty-six hours following the accident. A brief attack of cystitis soon cleared. On admission there was nervous tension, residuals of headache and blurred vision, and heavy granulations with infection over the burns. She had never been anesthetized before.

On February 15, 1946, one week after admission, the granulations were excised. Morphine sulfate 1/12 and scopolamine 1/300 grain were given subcutaneously two hours before operation. Cyclopropane induction, accompanied by moderate excitement, was done with closed to and fro absorption technic. Second plane anesthesia was maintained with ether and oxygen for the following thirty minutes. Although the blood pressure just before induction was recorded as 115/80 mm. mercury, no more readings could be obtained after ether administration was begun. The pulse rate rose from 95 per minute to 145, then decreased to 120. Respirations remained about 20 per minute. During ether administration, it was noted that the skin had become markedly flushed and "goose flesh" in character, ears and lips swelled moderately, and the skin of the wrists and fingers blanched white below the flexed joints. Recovery progressed to permit retching in operating room.

Twelve days later skin grafting was done: atropine 1/150 grain was given one hour and fifteen minutes before induction. She was nervous and had reddish blotches on her skin when she came to the operating room. The pulse rate of 150 per minute could be counted with ease and the blood pressure was 120/80 mm. mercury. Induction and maintenance of light anesthesia was accomplished without incident, using cyclopropane, nitrous oxide and oxygen in a closed to and fro absorption system. The plane of anesthesia was sufficiently light to permit coughing on several occasions. The reddish blotches soon disappeared and the patient's condition remained satisfactory with easily readable blood pressure and palpable pulse during the one hour and twenty minutes of operation. At the close cyclopropane and nitrous oxide were discontinued, and a test of ether was given by bubbling 400 cc. of oxygen per minute through an ether bottle into the closed system. Within ten minutes, essentially the same condition developed as during the first ether administration. The mask was then removed. Peripheral pulse and blood pressure were not obtainable, precordial heart rate was 180 per minute, respirations were 80 per

minute and short and jerky in character, pupils were 2/3 dilated, and the skin had a scarlet flush and a bumpy "goose flesh" surface. The skin was warm and dry and the patient's condition seemed better than the pulse and blood pressure indicated. Recovery was slow. Respirations were normal in fifteen minutes and pharyngeal reflexes were present in twenty-two minutes. When returned to the ward forty-five minutes after stopping ether, she was still unconscious, the skin remained flushed, respirations were 26 per minute, temporal pulse rate was 180 per minute, but neither radial pulse nor blood pressure could be recorded. Two hours later, the blood pressure was 80/60 mm. mercury, pulse 124 per minute, respirations 18 per minute. The remainder of the recovery was uneventful.

Because the untoward reactions in both anesthetic administrations are believed to be due to ether, the patient was advised to warn her physician of these experiences in case an operation is contemplated in the future.

DONALD R. KINDSCHI, M.D.,
Department of Anesthesia,
Wisconsin General Hospital,
Madison, Wis.

CORRESPONDENCE

COMMUNICATION FROM SECRETARY-TREASURER OF THE AMERICAN BOARD OF ANESTHESIOLOGY, INC.

Notification has been received of the following:

1. Dr. Ralph M. Waters resigned as a member of the American Board of Anesthesiology, Inc., representing the American Society of Anesthesiologists, Inc., to take effect at the termination of the October, 1946, meeting. Dr. Waters' resignation was regretfully accepted, and his unexpired term to January 1, 1950, was filled, in accordance with the Constitution of the American Board of Anesthesiology, by election from a list of three nominees selected by the Nominating Committee of the American Society of Anesthesiologists, Inc. Dr. R. J. Whitacre, of Cleveland, was elected by secret ballot.

2. Dr. H. Boyd Stewart resigned as a member of the American Board of Anesthesiology, Inc., representing the Section on Anesthesia of the Southern Medical Association, to take effect at the termination of the October, 1946, meeting. Dr. Stewart's resignation was regretfully accepted, and his unexpired term to January 1, 1950, was filled, again in accord with the Constitution of the American Board of Anesthesiology, Inc., by election from a list of three nominees, members of the Section on Anesthesiology of the Southern Medical Association. Dr. John W. Winter, of San Antonio, Texas, was elected by secret ballot.

These changes in the personnel of the American Board of Anesthesiology, Inc., were received from Dr. Paul M. Wood, Secretary-Treasurer of the American Board of Anesthesiology, Inc.

ERRATUM

To the Editor:

May I call your attention to a typographical error in my article in the current issue [March, 1947] of ANESTHESIOLOGY? On page 172, line 4, the fourth word reading "determination" should be "deterioration." This error seriously distorts the meaning, and I would like to request an erratum insert in the next issue.

Sincerely yours,

MILES H. ROBINSON, M.D.,
Laboratory of Pharmacology,
University of Pennsylvania,
Philadelphia, Pa.

ABSTRACTS

Editorial Comment: Material for this section is not abstracted in a uniform style. Many employ direct quotations only. Others are written in the more conventional form. At times there may be included a few opinions, personal to the abstractor, which, where they appear, will be bracketed or labeled "Comment." The Editorial Office continues in its desire to receive correspondence from readers relative to the management of this section.

BURDICK, D. L.; PHELPS, McK. L., AND PETERSON, M. C.: *Anesthesia for Sympathectomy in Hypertension.* New York State J. Med. **46**: 2139–2141 (Oct. 1) 1946.

Criteria for the selection of patients for operation for the treatment of essential hypertension vary in different clinics. Prognostic tests which will affect the sympathetic nervous system have only added to the differences in the selection. Loss of muscle tone and modifications in respiration may produce a false prognostic picture. Such is the case with spinal anesthesia, avertin and intravenous pentothal sodium. Recent reports of the use of continuous caudal anesthesia seem hopeful not only in selection of the patients but also in indicating the extent of surgery necessary for the desired result in each individual case.

With more extensive surgery now being used, the anesthetic management becomes more important. The technics may involve a longer operating time and an open chest. Adequate oxygenation must be insured. Intratracheal anesthesia, light premedication and controlled respiration when indicated are parts of the present management of these patients. Periodic inflation of the collapsed lung should be done throughout the operation. Circulatory disturbances occur more often and with greater severity when the operation is extensive and prolonged. Pulmonary edema may develop. Neosynephrine continues to be the most valuable drug for treating disturbances of blood pressure. Infusion of 5 per cent glucose in saline or water is started and 0.02 Gm. (2 cc.) neosynephrine is added to each liter. Regulation of the rate of flow maintains a fairly even blood pressure. At the conclusion of the continuous intravenous administration neosynephrine 0.0013 Gm. (2 min.) is given as needed. Injection by the surgeon of procaine hydrochloride, 2 per cent, about the ganglia and chain as soon as they are exposed may help control the fluctuations of blood pressure which sometimes occur. The administration of plasma may prove deleterious, especially in the face of pulmonary edema. The treatment of pulmonary edema is manual positive pressure in the operating room and by positive pressure mask thereafter. Intravenous therapy should be regulated judiciously.

F. A. M.

KNIGHT, R. T.: *Combined Use of Sodium Pentothal, Intocostrin (Curare), Nitrous Oxide.* Canad. M. A. J. **55**: 356–360 (Oct.) 1946.

A combination of pentothal with curare and nitrous oxide and oxygen has been used. Pentothal, probably the best hypnotic we have ever had, does not provide adequate relaxation unless administered in doses which pro-

duce depression. Nitrous oxide has moderately good analgesic properties but is a weak anesthetic. Thirty per cent oxygen should be given to the patient under anesthesia to insure safety and good physiologic effect. Curare in the form of intocostrin disconnects the myoneural junction, thus producing relaxation. It may also produce some degree of analgesia in larger doses. Curare is used with cyclopropane. Pentothal and curare are both administered intravenously. Various proportions of the two drugs have been tried. "The proportion that has worked most satisfactorily is 10 units of intocostrin with each 25 milligrams of sodium pentothal." "The sodium pentothal has customarily been used in 2½ per cent solution. Translated into volume, this proportional administration is 1 cc. of intocostrin to each 2 cc. of 2½ per cent sodium pentothal. This ratio is administered from the very beginning of induction, 2 cc. of 2½ per cent sodium pentothal followed by 1 cc. of intocostrin, this quanity of both being repeated at short intervals until the patient becomes unconscious. Half of the above quantities is then administered intermittently until the desired plane of anaesthesia is reached. In the meantime, as soon as the patient loses consciousness, the anaesthesia mask is applied, the bag having previously been filled with a mixture of ⅔ nitrous oxide and ⅓ oxygen. The flow is then continued at 500 cc. each of nitrous oxide and oxygen per minute."

The anesthetic mixture can be used for any type of surgery. The mixture is non-inflammable and non-explosive. Hiccups have occurred in about one in 15 or 20 patients. This has been controlled by "controlled respiration" or the addition of a small amount of cyclopropane. Increased sodium pentothal-curare stopped the respiration and the hiccup. Respiration was then carried on by compression of the bag. Intratracheal tubes have been inserted after the induction with pentothal-curare. Relaxation was adequate. Pentothal and curare are kept separate from each other because they precipitate. After injecting either one of the drugs the tubing and needle are washed down with a small amount of physiologic saline, 5 per cent dextrose or blood transfusion.

F. A. M.

SULKIN, S. E.; ZARAFONETIS, CHRISTINE, AND GOTH, ANDRES: *Influence of Anesthesia on Experimental Neurotropic Virus Infections. I. In Vivo Studies with the Viruses of Western and Eastern Equine Encephalomyelitis, St. Louis, Encephalitis, Poliomyelitis (Lansing), and Rabies.* J. Exper. Med. **84**: 277–292 (Oct. 1) 1946.

Past attempts to find an adequate method for the treatment of the neurotropic virus diseases have been largely unsuccessful. The ideal agent would destroy the virus without causing permanent injury to the host cell and should have the same tissue predilection as the virus. General anesthetics seem to fall in this category. Some experiments have been done on the effects of some anesthetics on certain toxic diseases affecting the central nervous system. It was decided to investigate the effect of anesthesia on those diseases already studied as well as others.

The virus of Eastern equine encephalitis was shown to be destroyed by ether. "Anesthesia with diethyl ether significantly alters the course of experimental infections with the equine encephalomyelitis virus (Eastern or Western type) or with the St. Louis encephalitis virus. No comparable effect is observed in experimental infections with rabies or poliomyelitis (Lansing) viruses. The neurotropic virus infec-

tions altered by ether anesthesia are those caused by viruses which are destroyed in vitro by this anesthetic, and those infections not affected by ether anesthesia are caused by viruses which apparently are not destroyed by ether in vitro. Another striking difference between these two groups of viruses is their pathogenesis in the animal host; those which are inhibited in vivo by ether anesthesia tend to infect cells of the cortex, basal ganglia, and only occasionally the cervical region of the cord. On the other hand, those which are not inhibited in vivo by ether anesthesia tend to involve cells of the lower central nervous system and in the case of rabies, peripheral nerves. This difference is of considerable importance in view of the fact that anesthetics affect cells of the lower central nervous system only in very high concentrations. It is obvious from the complexity of the problem that no clear-cut statement can be made at this point as to the mechanism of the observed effect of ether anesthesia in reducing the mortality rate in certain of the experimental neurotropic virus infections. Important possibilities include a direct specific effect of diethyl ether upon the virus and a less direct effect of the anesthetic upon the virus through its alteration of the metabolism of the host cell." 34 references.

F. A. M.

HEWER, C. L.: *Recent Advances in Anaesthesia.* Brit. M. J. **2**: 531–532 (Oct. 12) 1946.

The science and art of anaesthesia is now over one hundred years old, but it is convenient and useful to compare the state of the specialty as it was after the war of 1914–18 with that at the present time. At the beginning of the period selected preoperative starvation and purging were common practice. Premedication was confined to subcutaneous morphine and atropine. The anaesthetics in common use were nitrous oxide, ether, chloroform and ethyl chloride. Oil-ether rectal anaesthesia and intravenous ether in saline were occasionally used. Local anaesthesia was used, especially on the continent. Spinal analgesia was confined to hypobaric solutions and little was known as to controllability.

In the quarter of a century since the end of the war (1914–18) the preparation of the patient has been directed toward putting him in the best possible condition. Intravenous fluids, blood transfusion, adequate provision of food and drink and minimum purging are among the preoperative preparations. Premedication is now calculated for each patient and may include basal narcosis. Anesthesia may be started with intravenous induction. New volatile anaesthetics include ethylene, propylene, acetylene and cyclopropane. Of these cyclopropane alone has gained a permanent place in England.

New ethers include one which has attained popularity, divinyl ether. Trichlorethylene is a new volatile agent now in general use. Curare, as used in anaesthesia, "seems likely to mark the greatest advance in recent years." Apparatus for the administration of anaesthetics has developed considerably. The endotracheal technic has changed radically. The technic of controlled respiration is a recent development.

Local analgesia covers a wide field. New drugs for local analgesia which have attained popularity in Great Britain include nupercaine and amethocaine. Refrigeration of limbs has proved useful for amputations. Spinal analgesia has undergone many changes. Extradural spinal block has become more popular. Curare may replace high spinal analgesia in the future. The care of the patient's general con-

dition during operation is one of the duties of the anaesthetist. Intravenous fluids, newer analeptics, new methods of blood pressure determination and better records all aid in this objective. The ability of the anaesthetist is more important than new agents and technics.

F. A. M.

UNDERWOOD, E. A.: *Before and After Morton: A Historical Survey of Anaesthesia.* Brit. M. J. **2**: 525–531 (Oct. 12) 1946.

Many of the forerunners of the discovery of anaesthesia were British. October 16, 1946 is the centenary of the advent of surgical anaesthesia as a practical measure. The word anaesthesia was first used by Bailey in 1721. In 1829 it was used by Reid as synonymous with "loss of sensation." The New English Dictionary (Oxford) gives the earliest use of the word "anaesthetic" as by J. Y. Simpson in 1847. Oliver Wendell Holmes wrote to Morton to suggest that the state should be called "anaesthesia," from which the adjective would be "anaesthetic." Knowledge of prehistoric attempts to produce anaesthesia is speculative. Early civilizations have left some evidence that methods for producing insensibility to pain were being sought. Early pioneers of inhalation anaesthesia include Humphry Davy who suggested that nitrous oxide might "probably be used with advantage during surgical operations in which no great effusion of blood takes place." His suggestion was not followed up. Henry Hill Hickman suggested the use of "suspended animation" in surgical operations. He experimented on animals, after inducing a "torpid state," by allowing them to rebreathe their own exhaled air or by passing carbon dioxide into the bell-jars from which air was excluded. In the United States W. E. Clarke, Crawford W. Long, Horace Wells, W. T. G. Morton, and C. T. Jackson all contributed to the early use of anaesthetics for surgical operations. In England Robert Liston, John Snow, Joseph Clover, and James Young Simpson were pioneers in the development of anaesthesia. An exhibition at the Wellcome Historical Medical Museum, illustrating the whole history of anaesthesia, was opened on October 16, 1946. 33 references.

F. A. M.

DEBOER, BENJAMIN: *Water and Salt Exchange During Chronic and Acute Dehydration in the Dog.* Am. J. Physiol. **147**: 399, 1946.

The purpose of the investigation was to determine the changes in the water and chloride content of the skin and musculature during a period of chronic dehydration and recovery, and to compare these changes with those occurring in these organs with acute dehydration as a result of hemorrhage. Thirteen dogs were used in this study.

Dehydration by withholding food and water was followed by a greater loss of water from the skin than from the muscles of the body. Acute dehydration resulted in a similar but smaller loss of water from the skin. The chloride content of the skin increased from an average of 297 mg. sodium chloride per 100 cc. water to 440 mg. after chronic dehydration. The chloride content of the muscle deviated much less. In acute dehydration a slight increase in the chloride content of the skin occurred, while muscle tissue showed a decrease in chlorides. Acute hemorrhage in two dogs at the height of chronic dehydration produced slight deviation of the water content of the skin and muscle and a decreased chloride content of the muscle.

The results indicate that during chronic dehydration muscle tissue

shifts isotonic extracellular fluid to the circulatory system, whereas the skin loses chloride-free water and actually increases its chloride content. After hemorrhage, however, the isotonicity of the blood is maintained by obtaining water chiefly from the skin and chlorides from the musculature. The experiments involving acute dehydration at the height of chronic dehydration suggest that the conservation of fluid had reached a degree where tissues did not yield fluid even under stress of rapid hemorrhage.

M. F. P.

RUSKIN, SIMON: *The Control of Muscle Spasm and Arthritic Pain through Sympathetic Block at the Nasal Ganglion and the Use of Adenylic Nucleotide; Contributions to the Physiology of Muscle Metabolism.* Part II. J. Digest. Dis. **13**: 311, 1946.

The striking and dramatic relief of painful muscle spasm and arthritic pain through anesthetization of the sphenopalatine ganglion by topical treatment presented a challenge for its interpretation. The problem was approached on the thesis that the underlying biochemistry of contractile elements which would characterize all muscle spasm would tend to be the same.

The chemistry of muscle contraction underlies the basic physiology of nutrition. The keystone of muscle metabolism is adenylic nucleotide. It phosphorylates thiamin to cocarboxylase, thus making the biologically active coenzyme. Similarly, it phosphorylates riboflavin and combined with nicacinamide, it goes to form Coenzyme I and II. These are the factors that control cell respiration, for the coenzyme together with the amino acids of the protein portion form the respiratory enzymes (the enzymatic means whereby carbohydrate is gradually broken down by the stepwise removal of hydrogen and the liberation of energy). It is the deficiencies of the elements of the respiratory enzymes that produce the classical picture of vitamin deficiency.

Muscle metabolism requires, in addition to this energy releasing enzymatic setup, a substance that is uniquely capable of changing its molecular structure so as to alternately contract and return to its original form and utilizing for this purpose the energy released by tissue respiration. Such a substance is myosin, composed of a protein that is also bound to adenylic acid to form the enzyme adenointriphosphatase.

The basic idea that develops from the chemical study of muscle contraction is the uniformity of the reaction of all types of muscle. The clinical implication of this conception is the intimate relation between the spasm of large voluntary muscles and those of the heart and blood vessels, and the possible unity of the etiologic factor.

Confirmation lies in the success of the therapeutic use of adenylic nucleotide as the iron salt. The factors that tend to throw the balance of the chemical reaction in muscle metabolism toward the maintenance of the contracted state with incomplete recovery are the keys to the therapy of muscle spasm.

Our next consideration is the reflex neurogenic factor in muscle spasm. The idea of interrupting reflex autonomic factors by surgical attack on the adrenal sympathetic system demonstrated the ability to control muscular vasospasm in a lasting manner. Similar results may be obtained through blocking at the sympathetic sphenopalatine ganglion. The neurological connections of the nasal ganglion are pointed out.

We still have to consider what constitutes muscle spasm. A muscle

fiber stretched beyond its normal relaxation does not return to its initial length. A delta state is produced. Some active process of relaxation occurs in a normal muscle. This is abolished in the delta state. No answer has yet been found to the correction of the delta state of myofibril contraction. Sympathetic block seems to provide one of the first steps in this direction. Sympathetic block at the nasal ganglion appears to permit normal acetylcholine action. The restoration of muscle tone appears to be further heightened by parenteral use of the adenylic nucleotide as the iron salt. This would tend to indicate that adenylic acid is related to active relaxation as well as to active contraction.

The muscle cell can be stimulated to contraction, thereby bringing about development of mechanical energy and of electrical energy, which provides a mechanism for conduction of a contraction wave from one end of the muscle to the other. This electrical change can be resolved into various parts comparable to the spike and after potentials of nerve. Of particular significance are the potentials associated with activities at the myoneural junction.

It is by way of the sympathetics that we must search for the influence on the electrical potential of muscles induced by anesthetics, particularly the local anesthetics.

The problem of muscle tension is intimately bound up with muscle mechanics and represents a new chapter in physiology.

The third division of muscle physiology is the neuroeffector system. Adenylic nucleotide plays the basic role in muscle dynamics and thermodynamics. The chemical factors which play a role at the myoneural junction are acetylcholine and sympathin and adrenine. Now therapeutically, the anesthetization with cocaine, novocaine, or nupercaine of a sympathetic nerve center (sphenopalatine ganglion) is followed by immediate general relaxation of the muscle spasm not only of smooth muscle but of striated skeletal and syncytial cardiac muscle. This effect is not obtained by systemic administration of the anesthetic solution in the dosages used, but is profound when applied directly to the sympathetic nerve center. The degree of this effect can readily be compared with the surgical intervention on the adrenomedullar sympathetic system.

Cocaine and preganglionic denervation enhance the mechanical while depressing the electrical responses of muscle. Similarly, the injection of the iron salt of adenylic nucleotide, ferrous adenylate, increases the mechanical response of muscle fiber through making available immediately the energy-rich phosphate, and enhances the capacity of the muscle to overcome the spasm, possibly by active relaxation.

Indications for this block: 1. Painful muscle spasm (sacroiliac, torticollis, etc.) ; 2. Acute arthritic and chronic osteoarthritic pains; 3. Hypertension and peripheral vascular spasm; 4. Coronary pain; 5. Migraine and hemicrania; 6. Herpetic pain; 7. Spasmodic hiccups and sneezing; 8. Menstrual pain; 9. Uteral colic; 10. Intercostal neuralgia; 11. Spastic stage of poliomyelitis.

The dramatic nature of the results is its greatest handicap.

M. F. P.

APGAR, VIRGINIA: *Experience with Curare in Anesthesia.* Ann. Surg. **124**: 161–166 (Aug.) 1946.

Two hundred consecutive cases received curare during anesthesia. Intocostrin was the drug used. The intravenous route was used and the rate of injection was rapid. The maximum action was usually present in sixty sec-

onds and the duration varied greatly. There were 15 deaths, 2 of which occurred in the operating room. Eleven of the deaths were felt to be unrelated to the curare; 2 were unexplained and 1 of these may have been due to respiratory obstruction shortly after return to bed. One 4-day-old female was given curare and infiltration anesthesia for operative relief of atresia of the jejunum. No premedication was given. Respiratory depression developed during the administration of curare. The dose selected was 10 mg. Efforts to support the respiration by various means were unsuccessful and the heart, which seemed unaffected as long as the patient could be oxygenated, failed after more than two hours. Autopsy revealed that the brain tissue contained 0.25 mg. of curare per 200 mg. of brain tissue. It was later discovered that 1 cc., or 20 mg., of curare had been given instead of the 10 mg. planned.

Pulmonary complications included bronchopneumonia, 2 cases; atelectasis, 2 cases, and mild bronchopneumonia in one of the fatal cases. The results in 25 tonsillectomies anesthetized with pentothal and curare were appreciably better than a parallel series of cases without curare. A reëvaluation of the signs of anesthesia would overcome the main disadvantage of the use of curare. It is suggested that the concentration of the drug be changed to 1 per cent (1 cc. = 10 mg.) to lessen the hazard of mathematical error. 8 references.

F. A. M.

McCUSKEY, C. F.: *Anesthesia for Emergency Surgical Procedures.* California Med. **65**: 93–95 (Sept.) 1946.

In emergency surgical procedures the clinical condition of the patient must be considered when the anesthetic is chosen. Good muscular relaxation is necessary for exposure, hemostasis and gentle handling of tissues. "Before an anesthetic agent is selected its pharmacologic action should be considered and this action correlated with the clinical condition of the patient. It is generally accepted that ether produces a general peripheral vasodilation and when carried to the lower planes, a depression of vasomotion is common. Pentothal sodium also produces a peripheral vasodilation. Spinal anesthesia and regional blocks produce vasodilation in the anesthetized area. Frequently there is a compensatory vasoconstriction in the unanesthetized area. The body's first reaction to blood loss or trauma preceding shock is a peripheral vasoconstriction. This is the automatic attempt of the body to maintain sufficient blood for the vital centers. Following the administration of blood or plasma to patients who have had a severe drop in blood pressure, the pressure may rise to 100 to 120 systolic. This rise may occur before the total volume of blood lost has been replaced and is only possible because of the peripheral vasoconstriction still present. The administration of an anesthetic which produces vasodilation at this time will produce an immediate severe drop in blood pressure."

Treatment of shock, adequate premedication and emptying of the stomach should precede the administration of an anesthetic. The type of replacement fluid indicated can be determined best by evaluating the hemoglobin, hematocrit volumes per cent and plasma protein content of the blood. There is no substitute for whole blood. If a person is to receive repeated transfusions, consideration of the Rh factor is essential. The symptoms of hemolytic transfusion reactions are: a sense of increased heat in the skin, headache, a sense of constriction in the chest, pain in the lumbar region, rigor and fever. The first 100 cc. of every transfusion should be given slowly and transfusion

stopped if any of the above symptoms appear. Excessive quantities of fluids may cause pulmonary edema. Two large needles should be inserted before surgery in patients who require immediate operation and in whom bleeding has not been controlled.

Clinical experience has shown that patients in shock do not tolerate spinal anesthesia well, nor do they tolerate deep ether or deep pentothal anesthesia. These contraindications are relative and depend on the care and attention of the anesthetist. Regional block offers the patient the greatest margin of safety. By relieving pain regional block may prevent the onset of shock. When block anesthesia is not adequate cyclopropane is the agent of choice for supplementary anesthesia. Procaine, intracaine and metycaine are the local anesthetic agents most often used. An overdose of any of these agents produces respiratory paralysis ahead of cardiac failure so there is usually time for resuscitative measures. Procaine usually produces anesthesia lasting ninety minutes, metycaine a longer period than procaine and intracaine one hundred eighty minutes. Because of the rapid onset of anesthesia and the duration the author considers intracaine the local anesthetic agent of choice. 1 reference.

F. A. M.

HINGSON, R. A.: *Anesthesia in Geriatric Practice.* Am. Practitioner **1**: 105–107 (Oct.) 1946.

The number of aged persons requiring anesthesia has increased with the extended life span. The degenerative diseases, diabetes, cancer, arthritis, heart and blood vessel diseases and kidney diseases are more prevalent in the older patients. Often the anesthesia and complications are of greater concern to the patient and to the surgeon than is the operation itself. The physiological preparation of the older patient is more important than the preliminary sedation. Hidden fears, often childish and unreasonable, may be discovered by friendly conversation. One and one-half grains of a barbiturate such as delvinal or seconal given at bedtime the night before operation assures a restful night. If pain is also present the barbiturate should be supplemented with an intramuscular injection of 50 mg. of demerol. Large doses of barbiturates may produce psychoses in the aged. In order of their safe effectiveness, codeine, gr. 1 (64 mg.) pantopon, gr. 1/3 (22 mg.), and demerol, gr. 3/4 (50 mg.) are the analgesics which have been most effective for older persons. Morphine is associated with too many unpleasant side-effects to be considered safe. Atropine occasionally produces tachycardia and tenacious secretions. The author has found the use of scopolamine gr. 1/150 a good supplement for the barbiturates or the recommended opiates.

Induction with general anesthetics should be pleasant and as speedy as possible. Hyperventilation with oxygen should be carried out for several minutes before the anesthetic is started. High oxygen concentrations should be used when gaseous anesthetics are used. Intravenous barbiturates are given in smaller doses in the aged than is necessary in the robust, young patient. Spinal and caudal anesthesia should be given in small fractional doses.

Only the minute-by-minute requirements of the patient should be administered to maintain anesthesia. Normal blood pressure and oxygenation should be present when the patient leaves the operating room. Care in the postoperative period should include provision of good airway, avoiding drafts, prophylactic administration of penicillin and replacing of blood by transfusions.

F. A. M.

HIMWICH, H. E., AND ETSTEN, B.: *Criteria for the Stages of Pentothal Anesthesia.* J. Nerv. & Ment. Dis. **104**: 407–413 (Oct.) 1946.

The neuro-anatomic allocation of the clinical signs in the various stages of pentothal anesthesia are grouped in four stages: "stage 1, clouded consciousness; stage 2, hypersensitivity; stage 3, surgical anesthesia, which, in turn, is divided into 3 planes: (a) light surgical, (b) moderate surgical and, (c) deep surgical; stage 4, impending failure." The brain may be regarded as consisting of five phyletic layers with specific allocations of function. The first layer consists of the cerebral hemispheres, the second is chiefly comprised of the sensory thalamus, the vegetative hypothalamus and the subcortical motor nuclei. The third layer consists of the midbrain, the fourth layer, the pons and upper medulla and the fifth layer includes the vital medullary centers. The clinical signs found in the various stages of pentothal anesthesia proved to be the results of a descending cerebral depression.

"The physiological mechanisms for the clinical changes are two-fold: (1) The march of the symptoms is based upon a metabolic inhibition of the brain starting with the cerebral hemispheres and gradually extending toward the medulla oblongata. (2) The depression of motor phenomena and of respiration is out of proportion to the cerebral metabolic inhibition and is ascribed in part, to a specific effect on nerve function." 28 references.

F. A. M.

MACINTOSH, R. R., AND MUSHIN, W. W.: *Recent Advances in Anaesthetics.* Practitioner **157**: 303–309 (Oct.). 1946.

After a stagnant period of nearly 100 years curare has been introduced dramatically into the practice of anesthesia to facilitate relaxation. Ease of administration enhances the value of the drug but may also increase its hazards. Respiratory paralysis is one of the disadvantages of curare. Artificial respiration and physostigmine are used in the treatment of an overdose. Another disadvantage is that it increases bleeding. This has not been reported by other writers but has been true in cases done or observed by the authors. The cause is unknown but may be due to the action of curare on the sympathetic ganglia or may be due to the diminished action of the thoracic pump, coupled with the fact that the cardiac output is unimpaired. The loss of signs of anesthesia and the general anesthetic effect of large doses of curare are two features of curare which must be kept in mind.

In operations on patients with inflammatory swellings in the neck or floor of the mouth a clear airway is imperative and the choice or condemnation of any particular anesthetic drug is of secondary importance. Artificial respiration presents no problems provided the airway is clear.

The inadvertent injection of pentothal into an artery instead of a vein causes immediate intense scalding pain in the forearm and hand, and has resulted in gangrene and amputation of arm, hand or fingers. This accident is more frequent than the reports would indicate and can be avoided by palpating the vessel before pressure is applied to the upper arm. Infusion into sternal marrow is of value as a means of introducing fluids, including anesthetics into the blood stream.

Continuous spinal analgesia involves technical difficulties or inconveniences which are justified only if the results are better than those afforded by more simple methods. Continuous caudal analgesia for midwifery is very effective when carried out by those skilled

both in obstetrics and in the performance of caudal puncture, but holds much hazard for the novice in either. In states of acute thyroid activity and established thyroid crisis the use of a spinal anesthetic, by paralyzing the adrenal gland improves the patient's chances. Care and common sense exercised when administering a spinal anesthetic should minimize the risk of infection with subsequent headache and more serious sequelae. Procaine administered intravenously is said to relieve many forms of pain in an effective, safe, and prolonged manner. Vascular spasm is said to be relieved by intravenous injection of this drug. 22 references.

F. A. M.

MIQUEL, OVIDIO: *The Effect of Chloroform and Ether on the Activity of Cholinesterase.* J. Pharmacol. & Exper. Therap. **88**: 190–193 (Oct.) 1946.

Several attempts have been made to explain the parasympathetic phenomena associated with general anesthesia through an action cholinesterase. Since there is no agreement in the evidence from different laboratories it was decided to carry out a number of experiments in an attempt to clarify the problem. As a result of these experiments it was concluded that "(1) Ether and chloroform in concentration corresponding to those attained during deep general anesthesia do not inhibit the activity of cat serum cholinesterase in vitro. (2) In cats the cholinesterase activity of the serum during deep anesthesia was not depressed. (3) Ether and chloroform in concentrations higher than occur in blood during deep anesthesia inhibit cholinesterase in vitro. (4) The action of ether in the high concentration used is partially reversible. (5) These observations, while not conclusive, support the hypothesis that the parasympathetic effects observed during general anesthesia from ether and chloroform are not due to the inhibition of cholinesterase." 4 references.

F. A. M.

REYNOLDS, V. J.: *Addition of Penicillin Sodium to Anesthetic Agent for Local Infiltration Anesthesia: Preliminary Report.* Am. J. Obst. & Gynec. **52**: 641–644 (Oct.) 1946.

Of 208 consecutive deliveries 169 patients required repair immediately following delivery. Of these, 116 were under local infiltration anesthesia and 53 under inhalation anesthesia. The results of seven repairs were unsatisfactory; three complete disruptions, one fistulous tract, and three partial disruptions. Twenty others were "disturbing" in that redness and edema developed within twenty-four to forty-eight hours, followed by separation of the skin edges, sloughing and sluggish healing. To eliminate the factor of infection the use of penicillin was considered. For 81 consecutive repairs a local infiltration was made of 1 per cent procaine hydrochloride in normal saline to which 250 units of freshly made penicillin sodium were added to each cubic centimeter of the solution. This solution was made fresh at the time of each delivery and an average of 45 cc. was injected into the vulvo-vaginal tissues. Two pudendal nerve blocks were also done. In 77 patients the repairs were considered excellent. In three the results were excellent except for one centimeter shallow separations of the skin at the distal angle. No redness, edema or slough occurred and all three were healed by the fourteenth day. In one patient a large submucosal hematoma required evacuation. Subsequent healing was satisfactory with no sign of infection. Following the use of one brand of penicillin seven patients developed

extravasation of blood into submucosal and subcutaneous tissues at the sites of injection. Actual discomfort during the injection was increased in 50 per cent of the patients. Postpartum symptoms referable to the perineum were less and the repairs were free of swelling, redness or discoloration. Postpartum check-ups showed the repair areas to have less scar, less tenderness and more elastic properties. 10 references.

F. A. M.

SMITH, O. F., AND DOUGLAS, R. E.: *Prolonged Endotracheal Oxygen.* Rhode Island M. J. **29**: 754; 756; 761 (Oct.) 1946.

A 19 year old male entered the hospital for treatment of a gun shot wound of the upper abodmen. He had received 16 mg. of morphine sulfate forty-five minutes before admission. He was drowsy but could be roused easily. He was given another 16 mg. of morphine with 0.4 mg. atropine sulfate at 12:45. At 1:55 he was given 20 mg. pontocaine plus 2.5 cc. 10 per cent dextrose solution between L_4 and L_5 through a hematoma in the tissues surrounding the point of exit of the bullet. Projectile vomiting occurred at 2:03 followed by cessation of respiration. No pulse, blood pressure or cardiac sounds could be obtained. Artificial respiration, aspiration of vomitus, intubation of the trachea and continued infusion of plasma and administration of oxygen were used in treating the condition. Fifty minutes later the corneal reflexes returned, followed by spontaneous respiration and return of palpable pulse. At 4:30 the patient complained of pain and he was given morphine 16 mg. Skin anesthesia was present to T_6. At 4:45 spinal anesthesia was repeated using 150 mg. procaine between T_4 and T_5. Operation was performed, blood and plasma being given throughout. At the end of a month the patient was returned to the United States, his recovery having been uneventful. The repetition of the spinal anesthetic needed courage but no other anesthetic was available. The recovery after such a long time with no sign of life demonstrates the value of prolonged effort in resuscitation. 8 references.

F. A. M.

DICKMAN, R. W.: *Neonatal Deaths Following Term Deliveries, 1937–1945; Cause and Effect Relationships.* Minnesota Med. **29**: 783–790 (Aug.) 1946.

At St. Mary's Hospital in Duluth, Minnesota, a review of births since 1937 was undertaken to determine the causes of newborn mortality. A review of the literature was then made and correlated with the findings. Incomplete records made the study difficult. The total number of births at St. Mary's Hospital from January, 1937, until November, 1945, was 9,053. Of these 516 were premature deliveries. There were 80 deaths in full-term deliveries or .93 per cent, and there were 141 deaths among premature deliveries or 27.32 per cent. The number of stillborns for the period was 177. These figures compare favorably with reports in the literature except for the premature deaths in which the number in this series was greater than those reported.

Intracranial hemorrhage is the cause for the highest number of deaths in this series and is second in the literature. Anoxemia was the second highest cause of deaths in this series. An analysis of anesthetics was not attempted due to inadequate records. Lowest fetal mortality follows local infiltration anesthesia. Nitrous oxide and oxygen, given only with pains, is a safe anesthesia. Demerol is used for

analgesia but as yet no report has been made on the relation of this drug to asphyxia of newborns. If respiratory depression from analgesic drugs exists, then asphyxia will result as placental circulation decreases.

Asphyxia results in brain damage and atelectasis. Intratracheal intubation should be done on severely asphyxiated babies. Tubbing, manual artificial respiration, mouth to mouth insufflation and many other treatments of asphyxia produce varying and generally discouraging results. Administration of oxygen and carbon dioxide through an intratracheal tube at 10 to 12 mm. of water pressure and the intravenous administration of 1/20 to 3/20 gr. lobeline hydrochloride are advised for resuscitation of severely asphyxiated babies. A simple inhalator should be available for infants with mild asphyxia. 22 references.

F. A. M.

ANDERSON, A. F.: *Spinal Analgesia for Forceps Delivery in Abnormal Labour.* J. Obst. & Gynaec. Brit. Emp. **53**: 347–361 (Aug.) 1946.

Anesthesia for forceps delivery has received far too little attention. General inhalational anesthesia may be responsible for many avoidable fatalities and near fatalities following prolonged labor. A trial of spinal analgesia was undertaken in an attempt to avoid the disastrous results which have been observed after inhalational anesthetics. In 35 cases, most of which were prolonged labors with inertia, spinal analgesia was used. All injections were made through the 4th lumbar interspace with the patient in the sitting position. Spinal fluid was used to dissolve procaine crystals. The dose given was on the estimated difficulty of delivery. The patient remained in the siting position for five minutes after injection of the procaine. The benefit to the child was especially noticeable in prolonged labors. The danger to the baby from morphine narcosis with superimposed general anesthesia is avoided. As well as being a safe procedure spinal analgesia is important in preventing secondary shock and in minimizing hemorrhage and morbidity. 24 references.

F. A. M.

GILLETT, R. E.: *Continuous Spinal Anesthesia in Obstetrics.* Northwest Med. **45**: 743–747 (Oct.) 1946.

Spinal anesthesia was used for obstetrics as early as 1900 but the results were largely unsatisfactory. More recent reports show that with improved technics and less toxic anesthetic agents the results are better.

Using a continuous spinal technic, essentially the same as that described by Lemmon, a series of 500 cases was done. Of these 479 were normal and 21 were complicated deliveries. Ninety-five per cent of the anesthesias were satisfactory. In ten cases the results were partially satisfactory, supplementary inhalation anesthesia being necessary for delivery. Three per cent of the cases were completely unsatisfactory due to toxic reactions (7 cases), inadequate anesthesia (5 cases) and inability to perform lumbar puncture (2 cases). One maternal death was in no way due to the type of anesthesia. Fetal mortality, 2.1 per cent, was not related to the anesthesia.

Metycaine and pontocaine were the only drugs used. The needle was withdrawn, after injection of a small dose of the anesthetic solution, just before turning the patient into the delivery position. In 62 per cent of the patients the level of anesthesia was below the umbilicus and uterine contractions continued unabated. In the other 38 per cent the level of anesthesia was above the umbilicus and labor was slowed.

Pitocin was used when the progress of labor was slowed by the anesthesia. The pitocin was given in carefully graded doses. Nausea, vomiting, dizziness or headache occurred in 26 per cent of the cases. Adequate sedation, oxygen inhalation and dextrose solutions intravenously helped control these mild toxic reactions.

Mild headache followed delivery in 15 per cent of the patients. No infections or "back trouble" resulted. One patient developed a pain over the sacrum on the second day postpartum. A hyperemic area surrounded by a zone of hyperesthesia accounted for the discomfort. The pain and the lesion gradually disappeared. In three instances fetal tachycardia developed. The anesthesia was not discontinued and no deleterious results were encountered. 20 references.

F. A. M.

PARMLEY, R. T., AND ADRIANI, JOHN: *Saddle Block Anesthesia with Nupercaine in Obstetrics.* Am. J. Obst. & Gynec. **52**: 636–640 (Oct.) 1946.

Saddle block is a term applied to low spinal anesthesia confined to the perineal area. Nupercaine has been used with a high degree of satisfaction by many workers. Roman and Adriani simplified the technic for using nupercaine for general surgery by mixing it with glucose and have good results with saddle block for rectal, urologic and gynecologic surgery with nupercaine as the drug of choice.

In 136 obstetric patients nupercaine saddle block was used with gratifying results. The equipment for saddle block is the same as for any spinal anesthetic. The puncture is made, preferably in the fourth lumbar interspace, with the patient in the sitting position. A free flow of spinal fluid must be obtained to assure correct placement of the bevel of the needle in the subarachnoid space. As little spinal fluid as possible should be aspirated to avoid undesirable dilution of the anesthetic. After injecting the drug slowly the patient remains upright for thirty seconds, then she is placed in the recumbent position. Moving about is not permitted for the first five or ten minutes. When the patient sits up for thirty seconds a greater concentration of the drug localizes in the conus than if she is promptly allowed to assume the recumbent position. Uterine contractions continue but the patient must be told to bear down as she is unaware of the contractions. Two and one-half mg. of nupercaine (1/2 cc. of 1/200 solution) is mixed with 1/2 cc. of glucose solution. The average duration of analgesia was three hours. Pain of uterine contraction usually returned in three hours, but the perineum was still anesthetized. Complete relief of pain during labor and delivery occurred in 81 per cent of the patients. Inhalation of analgesic mixtures of nitrous oxide-oxygen was sufficient to relieve the dull ache which resulted in 14 per cent of the patients when forceps were applied or during traction. In 5 per cent of the patients anesthesia was unsatisfactory, probably due to faulty technic. The block was repeated after fifteen minutes and was successful the second time in every case.

The patients were comfortable and cooperative. In 68 per cent a single block was sufficient. In 32 per cent repeated blocks were necessary. Momentary fall in blood pressure, usually about 10 mm. systolic, was relieved by deep breathing. The hypotension with bradycardia, often seen with spinal anesthesia, occurred in only 3 cases. Ephedrine, intravenously, relieved these pressure changes. No respiratory depressions, rectal or urinary incontinence or postoperative headache was observed. No remarkable effect on the duration of labor was apparent. The

method is worthy of further clinical trial. 8 references.

F. A. M.

GOTTSCHALK, R. H.: *Respiration During the First Hour of Life.* Am. J. Obst. & Gynec. **52**: 651–656 (Oct.) 1946.

A study was made to determine if the use of demerol and hyoscine during labor exerted any action on the respiration of the newborn infant when given in dosages recommended by Roby and Schumann. Accurate information on the respiration of the newborn from the time of birth to one hour of age was also sought. A total of 68 records of respiration in 40 infants during their first hour of life and 53 records on 31 newborns whose mothers had received demerol and hyoscine, were obtained. Study of the records has shown that demerol and hyoscine, no matter when administered, exert no influence on the respiration of the newborn from 7 minutes to one hour of age. It was shown that a general anesthetic (ether and cyclopropane), when it is properly administered, has no effect on the respiration of the newborn after 7 minutes of age. 3 references.

F. A. M.

TAYLOR, E. S.: *Anesthesia and Analgesia in Obstetrics.* Northwest Med. **45**: 740–743 (Oct.) 1946.

Obstetrics is advertised by the lay press and the lay grape-vine, not for the low stillbirth rate, low incidence of eclampsia, postpartum hemorrhage or cesarean section, but exclusively for the relief of pain during labor. A moderate amount of pain is normal and everything compatible with safety for the mother and baby will be done by the obstetrician.

Morphine and scopolamine in small doses can be used for analgesia but this combination of drugs is not satisfactory in multiparous labors, in inertia cases, in premature labors or in multiple pregnancies. Demerol with scopolamine is probably the most satisfactory all-purpose analgesia for labor. When labor is established and the patient begins to mind her pains, demerol, 100 mg., scopolamine, gr. 1/150, is given. Forty-five minutes later scopolamine, gr. 1/150, is repeated. Demerol, 100 mg., is repeated every four hours. Scopolamine, gr. 1/200, is given each two hours. Restlessness results from the scopolamine so the patient must be attended. Intramuscular or intravenous administration of demerol is best. Demerol without scopolamine is less effective but should be used when supervision is not adequate. The barbiturates do not relieve pain; they produce amnesia. With scopolamine the barbiturates produce amnesia in 85 per cent of cases. Respiratory complications in the mothers are fairly common following barbiturates and scopolamine and also after paraldehyde. Continuous caudal anesthesia requires constant attendance of an expert anesthetist, is not suitable for many cases and is not without danger. For the delivery stage inhalation and local anesthesia are being used the most. Of the inhalation anesthetics, ether is the safest. Chloroform is a valuable anesthetic if it is used with caution. Nitrous oxide is a good anesthetic for the delivery. Prolonged general anesthesia is dangerous to the mother and the baby.

Pudendal block anesthesia for delivery and repair is the perfect anesthesia for the patient, the baby and the doctor. Practice will improve the technic of the operator and one can expect as high as 95 per cent of successful pudendal blocks. Local anesthesia for cesarean section is excellent and safe. Too little information is available as to the blood saving qualities of local anesthesia in obstetrics. 8 references.

F. A. M.

KINDSCHI, J. D.: *Caudal Analgesia for Obstetrics in Private Hospital.* Northwest Med. **45**: 747–750 (Oct.) 1946.

Skepticism was the first reaction to continuous caudal anesthesia but reassurance of neurologists and neurosurgeons, and the encouragement of the obstetric nurse persuaded the author to try this technic for obstetric anesthesia. First attempts were highly unsuccessful. As technical difficulties were overcome the incidence of failures decreased; as the advantages became more apparent improvement and continuation of efforts were decided upon. In a group of 275 cases no fetal or maternal deaths were attributable to the caudal block. Metycaine 1.5 per cent in Ringer's solution was used in all cases. Shortening of labor and relief of pain resulted. In a second series of 1,065 deliveries, 1,003 were done under caudal anesthesia with only 2.5 per cent failures as compared to 23 per cent in the first group. One fetal death in the second series was attributed indirectly to the anesthesia; only 38 cc. of solution was used with anesthesia reaching to the third dorsal level. Circulatory depression and anoxia of both mother and fetus followed. One maternal death occurred. A caudal block was started in an obese gravida-five in premature labor with ruptured membranes and left saphenous phlebitis with multiple varicosities. The caudal block was started with the patient in the knee-chest position because of her obesity and an obscure sacral hiatus. Metycaine, 30 cc. of 12.5 per cent solution, gave complete relief of pain. One-half hour later the patient complained of severe pain which she did not locate, and immediately after this a convulsion started. Blood pressure was 134/76. Respirations were slow and labored. She was delivered immediately of a baby who died ten minutes later. Blood loss during the delivery was replaced with two units of plasma. Oxygen and stimulants were administered but the patient died two hours later without regaining consciousness. Autopsy revealed no penetration of the dural sac and no pulmonary embolism.

Although seldom needed all of the safeguards, oxygen, plasma, ephedrine and intravenous barbiturates as well as coramine, caffeine and a sterile spinal needle should be ready. Postpartum care is simplified following caudal anesthesia and labor most nearly simulates labor as nature intended it to be. 3 references.

F. A. M.

TRENT, J. C.: *Surgical Anesthesia, 1846–1946.* J. Hist. Med. & Allied Sc. **1**: 505–514 (Oct.) 1946.

The present attitude of taking anesthesia for granted must be abandoned in order to comprehend the tremendous significance of the introduction of surgical anesthesia. The surgeons as well as the patients suffered from the horrors of operation without anesthesia. The presence of pain was a barrier to the development of surgery as a science. Surgeons throughout the centuries endeavored to find some means of alleviating pain. In prehistoric and classical times drugs were used to induce sleep and deaden pain. The true story of anesthesia began in 1772 with Priestley's discovery of nitrous oxide. Many hypotheses and experiments contributed to the history of anesthesia before Morton's demonstration in 1846. Some historians have come to disregard the controversy over the discovery of ether and to interest themselves in the development of anesthesia, the spread of its use and the emergence of its various branches.

New developments in anesthesia give promise that the future will bring even

greater achievements than the tremendous advances of the past one hundred years. 20 references.

F. A. M.

TALLMADGE, G. K.: *Some Anesthetics of Antiquity.* J. Hist. Med. & Allied Sc. **1**: 515–520 (Oct.) 1946.

The history of anesthesia begins with the first use of the poppy, the mandragora, the hyoscyamus, and alcohol in the relief of human pain. Poppy was used to produce sleep, to relieve cough, and to relieve pain. It was known to produce lethargy and death. Tears of poppy—opium, were well known. Hyoscyamus was known to be poisonous and to lack uniformity in its effects. It was generally combined with opium. Mandragora was used for surgical anesthesia for many centuries. Wild lettuce was used as a soporific. Mulberry, a species of hemp, was used by the Scythians, the Chinese and by surgeons of the Western world. It had a small reputation as a soporific. 1 reference.

F. A. M.

HORINE, E. F.: *Episodes in the History of Anesthesia.* J. Hist. Med. & Allied Sc. **1**: 521–526 (Oct.) 1946.

In 1846 sulfuric ether was demonstrated to be relatively safe as an agent for the alleviation of the pain of operations. The controversy concerning the discovery of the anesthetic properties of ether attracted attention which undoubtedly contributed to the rapid popularization of its use. Oliver Wendell Holmes deserves credit for the independent coinage of the words anaesthesia and anaesthetic; however, Dioscorides used the word anesthesia as well as rectal and local anesthesia. Mandragora and alcohol were used in early attempts to relieve pain. The demonstration of ether anesthesia by Morton was the culmination of a long period of research and discovery. In the books concerning anesthesia a surprising number of errors will be found. Coincidence also plays a part in the development of anesthesia. 23 references.

F. A. M.

ROSEN, GEORGE: *Mesmerism and Surgery; a Strange Chapter in the History of Anesthesia.* J. Hist. Med. & Allied Sc. **1**: 527–550 (Oct.) 1946.

Mesmerism in surgery was part of the mesmeric movement that began in England in 1837 under the leadership of John Elliotson. An Irishman, Chenevix, who gave demonstrations of mesmeric phenomena was asked by Elliotson to try mesmerism on certain patients at St. Thomas's Hospital in 1829. In 1837 a Frenchman, Dupotet became associated with Elliotson at the North London Hospital. Mesmeric demonstrations were soon the talk of London. Medical and lay persons flocked to the hospital. Opposition to Elliotson's demonstrations developed within the hospital and eventually resulted in Elliotson's resignation. He continued to demonstrate the truth of mesmerism. He and his sympathizers published a journal, "The Zoist: A Journal of Cerebral Physiology and Mesmerism, and their Application to Human Welfare." Jules Cloquet, a French surgeon, performed a mastectomy on a patient in mesmeric sleep in 1829. Reports of the use of mesmeric anesthesia for surgical operations, some from America, appeared in The Zoist. In America the opposition was not as vituperative as that of the British medical journals. James Esdaile read reports of Elliotson's activities and tried mesmerism in surgical cases. Esdaile later tried ether for anesthesia. The margin of uncertainty in producing anesthesia was greater with mesmerism than with ether and chloroform. The surgical use of mesmerism declined.

The mesmerists were hostile to ether and chloroform. They claimed that mesmerism was safer as an anesthetic agent. The advocates of mesmerism kept alive the interest in the subject and helped pave the way for the acceptance of chemical anesthetics. 89 references.

F. A. M.

KEYS, T. E.: *John Snow, M. D., Anesthetist.* J. Hist. Med. & Allied Sc. 1: 551–556 (Oct.) 1946.

John Snow was the "alpha" of physician anesthetists. Snow is remembered by some members of the medical profession for his investigations of cholera. His first medical paper, which he read in 1841, was on the subject of asphyxia and the resuscitation of stillborn children. Snow's monograph on ether was published in September, 1847. In the monograph he first published his observations on the stages or degrees of anesthesia. He divided the signs into four well known stages which are still recognized. In 1858, in his book on anesthesia, he described a fifth stage, intercostal paralysis. Snow developed anesthetic apparatus and was positive in his opinion as to the desirability of administering anesthetics by exact methods. He warned of the dangers of chloroform. The acceptance by Queen Victoria of chlorform analgesia assured its continued use in obstetrics. Snow made important observations on the use of chloroform and repeatedly warned of its dangers. After his death, his monograph, "On Chloroform and Other Anaesthetics: Their Action and Administration," was published. Snow searched for the perfect anesthetic, investigating many possibilities. Of the substances he tried, amylene seemed to come closest to his ideal. He administered it clinically in 238 cases but discontinued its use after the death of two of the patients. Modern anesthesia owes a debt to John Snow who was an indefatigable worker, a scientist of no mean ability and a searcher for the ultimate truths. 43 references.

F. A. M.

HEATON, C. E.: *The History of Anesthesia and Analgesia in Obstetrics.* J. Hist. Med. & Allied Sc. 1: 567–572 (Oct.) 1946.

Before the era of modern anesthesia, attempts were made to relieve the suffering of childbirth. The ideal agent for the relief of such pain has not been found. The advisability of complete analgesia and amnesia during labor has been questioned. Early efforts to relieve the pain of childbirth were met with opposition. Sir James Y. Simpson is credited with the introduction of modern anesthesia in obstetrical practice. He first used ether for childbirth on January 19, 1847, and on November 8 of the same year he used chloroform for the first time in an obstetrical case. John Snow administered chloroform to Queen Victoria for the birth of her eighth child. In the United States there was a long delay in the application of anesthesia for obstetrical purposes after it was used for surgical cases; however, a case was reported in April, 1847, in which letheon had been used in a case of labor. The principle American champion of the use of ether in childbirth was Walter Channing. Augustus Kinsley Gardner administered chloroform for the first time in this country for a normal delivery in February, 1848.

Nitrous oxide was introduced into obstetrical practice by Klikowitsch of Petrograd in 1880 and by Winckel of Dresden in 1881. Nitrous oxide and oxygen were used by J. Clarence Webster of Chicago in 1909. Scopolamine hydrobromide and morphine sulfate were introduced by von Steinbüchel in

1902 to produce amnesia and analgesia during the first stage of labor. The method, known as "twilight sleep," was abandoned because a high incidence of asphyxiated babies resulted from its use. The barbiturates were introduced into obstetrical practice in 1928. Many agents and methods have been introduced to produce painless childbirth. Gwathmey's synergistic analgesia, spinal, paravertebral, peridural and sacral anesthesia all have their advocates. The safest method is direct local infiltration. 12 references.

F. A. M.

LEAKE, C. D.: *Historical Notes on the Pharmacology of Anesthesia.* J. Hist. Med. & Allied Sc. **1**: 573–582 (Oct.) 1946.

Pharmacology as a scientific discipline has developed during the last hundred years although various drugs had been applied to the relief of pain since the beginning of civilization. Semi-pharmacologic studies on such gases as oxygen and nitrous oxide began with the development of modern chemistry. Humphry Davy and Henry Hill Hickman conducted such experiments before the demonstration of nitrous oxide for surgical anesthesia by Horace Wells and of ether by W. T. G. Morton. After these practical demonstrations of anesthesia, pharmacologic studies of anesthetics began. In 1847, Flourens reported crude studies on the anesthetic properties of chloroform in comparison with ether. Pirogoff studied etherization and Simpson made an extensive survey of ether and chloroform. J. F. M. Heyfelder studied ethyl chloride as an anesthetic. John Snow made systematic pharmacologic studies on anesthetic agents. His student, B. W. Richardson, studied the comparative toxicities of various alcohols, ethers, and other hydrocarbon compounds. Claude Bernard made an analysis of anesthetic agents and proposed the first theory of the mechanism of action of anesthetic agents in incomplete reversible coagulation of protein. In 1806, F. W. A. Sertürner isolated a chemically pure, crystalline compound from opium. This was named morphine. Cocaine has been isolated from coca leaves, and Carl Koller studied this drug and introduced it as a local anesthetic. R. Willstätter determined the chemical constitution of cocaine and this led to the further study and chemical modification of the drug which in turn led to the introduction of other local anesthetic agents. A. Einhorn developed "novocaine" which, under the public name of procaine, is the least toxic and most effective local anesthetic for infiltration anesthesia.

Quantitative methods in studying anesthetic agents were developed slowly but many workers have contributed to these studies. The effect of various general anesthetic agents on metabolism and devices for measuring the content of these agents in the tissues have been developed. Ethylene was rediscovered. Cyclopropane was discovered. The anesthetic properties of divinyl oxide were predicted before the agent was produced. Further studies are being made among the unsaturated and unsymmetrical hydrocarbon ethers. The barbitals were vigorously explored under excessive commercial competition. The central depressant action of the alcohols were also studied, with the addition of halogens. Avertin was one of the results of these studies. Many pharmacological studies on the mechanism of anesthesia have resulted in brilliant hypotheses, without much substantial evidence in conclusive support of any particular one. As yet we do not know how anesthetics act nor what pain is.

F. A. M.

GILLESPIE, N. A.: *The Evolution of Endotracheal Anaesthesia.* J. Hist. Med. & Allied Sc. **1**: 583–594 (Oct.) 1946.

Andreas Vesalius showed that the lethal effects of pneumothorax could be avoided if the lungs were rhythmically inflated by blowing air into the trachea by means of a reed or tube. The literature contains many allusions to the use of tubes placed in the trachea for purposes of resuscitation. John Snow administered an anesthetic to a rabbit through a cannula tied into a tracheotomy opening. In 1869, Friedrich Trendelenburg applied Snow's technic to the human being, using an inflatable cuff around a tube. William Macewen of Glasgow first used true endotracheal anesthesia. He used a metal tube which was introduced into the trachea by the sense of touch. Macewen abandoned the method after the death of a patient. During the latter part of the nineteenth century several workers began to use endotracheal anesthesia in occasional specific cases of especial difficulty. Franz Kuhn began to use the method seriously and consistently. He appreciated all the possibilities of intubation such as the prevention of foreign material being aspirated into the trachea and using the tube as a means of removing secretions. Barthélemy and Dufour of Nancy, in 1907, used the technic which has become known as "endotracheal insufflation." Meltzer and Auer carefully investigated insufflation and encouraged C. A. Elsberg to apply it to the human subject. Elsberg preached and practiced the use of Chevalier Jackson's laryngoscope for introducing the endotracheal catheter. In 1913, Jackson advocated laryngoscopic intubation. Development of machines to administer anesthetics and skill in intubation has increased the usefulness of the endotracheal technic. 45 references.

F. A. M.

WATERS, R. M.: *The Development of Anesthesiology in the United States: Personal Observations 1913–1946.* J. Hist. Med. & Allied: Sc. **1**: 595–606 (Oct.) 1946.

"The foundation of any specialty is dependent, I suppose, first upon men, second upon publications, and third upon organizations through which men meet for mutual development by exchange of ideas. . . . In January, 1913 I began the general practice of medicine in Sioux City, Iowa. . . . A majority of us, occasional 'surgeons,' depended upon each other to act as anesthetist as occasions demanded. . . . Probably three reasons contributed to my early interest in, and special attention to anesthesia. First, the results of anesthesia which I observed were variable and offered something of a challenge. Second, extra-curricular experience in the administration of anesthetics while a student in Cleveland, together with occasional opportunities to observe the use of nitrous oxide by the extremely skillful dentist, Charles K. Teter, had developed in me an unusual interest in the subject. And lastly, one of the more 'surgical' surgeons returned from an eastern trip in 1913 with a nitrous oxide apparatus (the first in Sioux City) the use of which he offered to me in other cases if I would anesthetize his patients. . . . A desire to study was the natural outcome of this enforced special interest. . . . It was with considerable joy, . . . that I discovered the introductory number of the Quarterly Supplement of Anesthesia and Analgesia appended to the October 1914 issue of the American Journal of Surgery. . . . Almost simultaneously with the appearance of the quarterly supplement, the textbook of Gwathmey and Baskerville became available. Gwathmey with McMechan's help had begun the organization of an American Association of Anesthetists in 1912. . . . Papers by Ira McKesson

had earlier attracted my attention. . . . Ira McKesson was the Toledo Technical Appliance Company. He led the life of a multiple personality. . . . It was through informal visits of McKesson and W. Hamilton Long of Louisville to McMechan's home, then in Cincinnati, that the Interstate Association of Anesthetists was organized. The first meeting was held in Cincinnati in 1915. . . . In 1916, the Surgery Publishing Company copyrighted the first of a series of American Yearbooks of Anesthesia and Analgesia to be edited by McMechan. . . . The second volume did not appear until 1920 and no further volumes exist. In the foreword to volume two . . . appears the following: So far no Anesthesia Foundation has eventuated although recently some forward-looking manufacturers of anesthetics and apparatus have united to finance a National Anesthesia Research Society which, it is hoped, if it can serve its expectations, will sooner or later become a foundation. The name 'National' was soon changed to 'International.' . . . The first number of Current Researches in Anesthesia and Analgesia appeared in August, 1922. It continued under the editorship of McMechan until his death in 1939. . . . In addition to the organization of the Interstate Association of Anesthetists (1915) McMechan's stimulus was instrumental in the initiation of other regional societies in many parts of the United States and one in Canada. The year 1926 was a memorable one both for the McMechans and for anesthesia in general. In that year the old American Association of Anesthetists became the Associated Anesthetists of the United States and Canada with the purpose of serving as a parent organization to the Interstate (its name now changed to Midwestern), the Canadian, the Pacific Coast, the Southern and the Eastern Associations. The Quarterly Supplement appearing with the American Journal of Surgery was discontinued in that year. . . . There is little doubt in my own mind that the contributions toward the abolition of pain in the world made by the McMechans from 1912 to 1930 were unequaled. Until 1930 we who are now considered 'older anesthetists' were content to delegate all the labor of organization and the conduct of organized effort to one man. The need for a Section of Anesthesia in the American Medical Association, for a National Board of Certification, for a modernized journal of anesthesiology and other advances was evident to those within and outside the specialty. . . . In casting about for a vehicle through which to apply newer methods . . . [the] old New York Society was expanded to become The American Society of Anesthesiologists, Inc. . . . Through the tremendous interest, enthusiasm and energy of Dr. Paul Wood, the reorganization and expansion was launched with a minimum of difficulties. . . . A Section on Anesthesiology is now included in the scientific sessions of the American Medical Association. A National Board of Anesthesiology, Inc. stands ready to certify as competent those anesthetists who pass its examinations. A creditable journal, Anesthesiology, is published six times a year by the American Society of Anesthesiologists, Inc." 2 references.

F. A. M.

NEVEU, RAYMOND: *The Introduction of Surgical Anesthesia in France.* J. Hist. Med. & Allied Sc. 1: 607–610 (Oct.) 1946.

In France, Jobert de Lamballe was the first to use ether for surgical anesthesia. He first attempted etherization on December 22, 1846, but was unsuccessful; however, he did succeed in anesthetizing a patient two days later. Malgaigne and Velpeau used ether and reported their cases in January of 1847.

Soon after these reports the use of ether was introduced in all surgical services throughout France. Much zeal and ingenuity were shown by physicians and manufacturers in contriving appliances for use in anesthesia. The use of ether in midwifery was reported in February, 1847. French physiologists studied the problem of anesthesia and contributed greatly to the improvement of anesthetic methods. Gerdy, Longet, Flourens, Figuier, Soubeiran and other names appear in the early contributions. Early reports of fatalities following the use of chloroform caused it to be abandoned in favor of ether. Improvement in technics made the use of chloroform safer and it was again used by the pioneers in surgical anesthesia. 2 references.

F. A. M.

FRANKEL, W. K.: *The Introduction of General Anesthesia in Germany.* J. Hist. Med. & Allied Sc. 1: 612–617 (Oct.) 1946.

It is not known through what channels the news of the use of ether for surgical anesthesia first reached Germany. Only a short time elapsed between the first use of ether for surgery and its use in obstetrics. Heyfelder was probably the first surgeon in Germany to perform surgical operations on patients anesthetized by ether. Schuh, Behrend, Halla and Hammer each used ether within a few months of its introduction in the United States, and its use by other physicians spread rapidly. VonSiebold's presentation of a paper on etherization contributed much to the acceptance of anesthesia, and his paper must be regarded as one of the classics of medical literature. The term "general anesthesia" was never accepted in Germany. Physicians called the method "Narcose." Chloroform became more popular than ether and its popularity continued until early in the twentieth century. 2 references.

WHITACRE, R. J., AND DUMITRU, A. P.: *Development of Anesthesia in Germany in the Early Years of the Twentieth Century.* J. Hist. Med. & Allied Sc. 1: 618–634 (Oct.) 1946.

Many of the technics and agents which have aided in widening the field of usefulness of anesthetics were first introduced in Germany. O. Witzel of Düsseldorf first advocated the use of ether by the open drop method. The endotracheal technic of administering inhalation anesthetics was pioneered by the German surgeon Franz Kühn of Cassel. He described most of the basic principles of endotracheal anesthesia as it is used today. Alfred Kirstein of Berlin invented a forerunner of the direct-vision laryngoscope. Gustav Killian of Freiburg modified Kirstein's laryngoscope and made it possible to pass a tube more easily into the trachea.

German investigators were pioneers in the development of local, spinal and regional anesthesia. In 1884, Carl Koller demonstrated the use of cocaine for local anesthesia of the eye and Jelinek of Vienna used it for anesthesia of the nose and throat. Carl Ludwig Schleich, in 1892, introduced a new technic of local anesthesia in an effort to increase the safety of injected cocaine by injecting low concentrations of local anesthetic drugs. Heinrich Braun, an early worker in the field of local anesthesia, suggested the use of adrenalin in local anesthetic solutions to decrease the rate of absorption of the drug. The German chemist, Alfred Einhorn synthesized novocaine which proved to have a low degree of toxicity and his became the standard by which other local anesthetics are evaluated.

In 1908 August Bier attempted to produce anesthesia by the intravenous infusion of procaine. In 1898 he combined the technics of Corning and Quincke to demonstrate the feasibility of producing surgical anesthesia by the

injection of anesthetic drugs into the spinal canal. Dönitz and Klapp each studied the use of vasoconstrictors intradurally.

In 1905, Hugo Sellheim of Leipzig first used paravertebral blocks. Kappis, in 1911 used the posterior approach to produce splanchnic block and in 1919, Braun advocated the anterior approach. In 1909 Läwen perfected a technic of injecting branches of the sacral nerves through the posterior sacral foramina.

Dresser, in 1899, introduced hedonal. Ludwig Burkhardt reported his experimentation with intravenous ether and chloroform in 1909. He also experimented with other drugs for intravenous anesthesia. The first barbiturate, veronal, was synthesized in 1902 by Fischer and von Mering. Bogendörfer reported the intravenous use of dial in 1924. Other barbiturates were reported. Weese and Scharpff, in 1932, introduced evipan which was immediately successful as an intravenous anesthetic. "Twilight Sleep" was introduced in Germany by von Steinbüchel in 1902. 57 references.

F. A. M.

LILJESTRAND, G.: *The Introduction of Surgical Anesthesia in Sweden.* J. Hist. Med. & Allied Sc. **1**: 635–640 (Oct.) 1946.

Before the telegraph had revolutionized international communication the diffusion of knowledge was slow. It was not until February, 1847 that the first reports of the use of ether for surgical anesthesia were read to the members of the Swedish Medical Society. Doctor C. J. Ekströmer was asked by the Medical Society to make experiments with ether. His report was read in March. Doctor E. G. Polmgren devised an apparatus to be used for ether administration. Doctors O. A. Swalin, V. Lundberg and others used ether within the first weeks after the reports of its use reached Sweden. Ether, and later, chloroform were used for obstetric practice soon after they were accepted for surgical anesthesia. 19 references.

F. A. M.

DEL REAL, E. G.: *Surgical Anesthesia in Spain.* J. Hist. Med. & Allied Sc. **1**: 641–643 (Oct.) 1946.

After hearing of Morton's demonstration of the anesthetic qualities of ether, Spanish physicians interested themselves promptly in the discovery. Diego de Argumosa y Obregon used ether for various surgical anesthesias beginning in February, 1847. Benavente, Ruiz Gimenez, and Ulpiano Fernandez inhaled ether vapor in their studies. Basilio San Martin was the first to observe and to point out the importance of antecedent alcoholism for the disturbances supervening during general anesthesia. Ether was used by Antonio Saez who administered a drachm of ether and an ounce of distilled water by enema before the patient was given inhalation ether. Vincente Guarnerio used chloroform eighteen days after Simpson published his discovery. In 1888, Professor Morales Perez began to use warm ether for anesthesia. He reported 4917 operations using this method, without having observed any respiratory complications. In 1896, Suarez de Mendoza used and recommended the use of a mixture of chloroform and oxygen, which he called the "Spanish method." 3 references.

F. A. M.

CARVALHO, A. D.: *The Introduction of Sulphuric Ether and its Substitutes in Portugal.* J. Hist. Med. & Allied Sc. **1**: 644–648 (Oct.) 1946.

In March, 1847, Adolphe de Mareille de Vitry, junior, a dentist in Lisbon advertised that he would use ether in

dental operations but there is no evidence of such use. In a book published in October, 1847, he refers to the first use of ether for a surgical operation in Portugal. The operation was done in May. In April Bernardino Antonio Gomes and A. P. Barral experimented with ether on two volunteer students. A. J. Pinheiro, a surgeon, used ether when extracting a tooth. Cardosa Klerk, Joaquin Augusto da Silva, J. Teotonio, Francisco Alberto d'Oliveira, J. M. Alves Branco, Oliveira Velho and L. P. Fonseca were among the physicians who used ether soon after its discovery. Others who contributed to the study of ether were Manuel Maria, Sousa Soares, Casado Giraldes, L. de Castro Carreira, J. R. Nuñes, F. Ferreira d'Abreau, J. M. Arnaut and João Felix Pereira. Many other physicians used ether and reported their experiences. Chloroform was tried by many surgeons. Amylene was used for anesthesia in 1852 by Casado Giraldes and later by other Portuguese physicians. Hypnotism was used by Portuguese surgeons for surgical anesthesia soon after it became known to them. Use of nitrous oxide was reported by Jearmel in 1869. 21 references.

F. A. M.

SÁNCHEZ, J. L.: *The Introduction of Anesthesia in Cuba.* J. Hist. Med. & Allied Sc. **1**: 649–656 (Oct.) 1946.

The first announcement of the discovery of ether reached Cuban physicians in an article in a daily newspaper on December 26, 1846. Vincente Antonio de Castro first used ether in surgical practice. During the year 1847 ether was used in almost all surgical operations in Cuba. Doctor Priu recommended a combination of morphine and ether. Doctor Nicolás J. Gutiérrez was the first to use chloroform. Cuban medicine was influenced by French example and chloroform continued to be preferred over ether from 1848 to 1916. 6 references.

F. A. M.

BORJA, V. P.: *Early History of Anesthesia in Ecuador.* J. Hist. Med. & Allied Sc. **1**: 657–661 (Oct.) 1946.

Testimony of doctors who graduated from the year 1888 on was used to study the history of anesthesia in Ecuador. In 1882 surgical patients were anesthetized with chloroform applied by compress. President Garcia Moreno, observing the backwardness of his country's institutions, invited Gayraud and Domec from France to revise the medical teaching system. These French surgeons introduced chloroform. Ether was introduced by Dr. Francisco Martínez Aguirre about 1890. Local anesthesia was used a few years after 1888.

F. A. M.

DURAN, C. M.: *From the Abyss of Pain to the Summit of Anesthesia.* J. Hist. Med. & Allied Sc. **1**: 662–666 (Oct.) 1946.

"Man has always suffered pain. . . . The fervor with which we today celebrate the centenary of the discovery of the anesthetic properties of nitrous oxide is nothing more than that constant eagerness which moves us to alleviate suffering and to ascend from the abyss of pain to the summit of anesthesia. . . . No one knows pain so well as the doctor. . . . I have always asserted, almost too strongly, that the great advances and discoveries of Medicine are due principally to the contemplation of human pain. . . . We cannot forget that anesthesia, first, and antisepsis and asepsis, later, were the two great developments which made possible the progress of surgery. . . . The discovery of the anesthetic properties of certain chemical substances was the product of chance and curiosity. . . .

It would be ungrateful if on this occasion, dedicated to the triumph over pain, I did not devote a few words to the history of anesthesia in Guatemala. It was exactly four years ago, in December, that we met in this blessed house of pain, which is called Hospital de San Juan de Dios, to celebrate the practice of ether anesthesia in Guatemala. There are the commemorative plaques to record the event. It was in this blessed house, always filled with suffering, rich in a tradition which reforming impulses are trying in vain to eradicate, that Dr. José Luna tested etherism on November 30, 1847. It was here also that the students of medicine, Juan José Cañas and Felipe Arana, offered for the sake of science to be anesthetized by ether."

F. A. M.

CORDOBA, SALVADOR: *The Introduction of Anesthesia in Venezuela.* J. Hist. Med. & Allied Sc. **1**: 667–669 (Oct.) 1946.

It is impossible to establish with certainty, from authenticated documents, either the date or the first use of anesthetics in Venezuela. According to Doctor Santiago Rodriguez Rivero, Blas Valbuena used ether as an anesthetic in Maracaibo in the year 1847. Vincente Peña, after studying the question concluded that a surgical operation performed May, 1849 by Eliseo Acosta, was the first in which chloroform was used.

F. A. M.

HUME, E. H.: *Peter Parker and the Introduction of Anesthesia Into China.* J. Hist. Med. & Allied Sc. **1**: 670–674 (Oct.) 1946.

Ether was introduced into China by the Reverend Doctor Peter Parker of the Canton Hospital in 1847. Chloroform was also used by this same Peter Parker soon after its introduction by Simpson. 9 references.

F. A. M.

UNVER, A. S.: *Notes on the History of Ether Anesthesia in Turkey.* J. Hist. Med. & Allied Sc. **1**: 675–676 (Oct.) 1946.

Ether was introduced into Turkey relatively late. Chloroform was preferred by physicians who were trained in France and ether by those who were trained in Germany.

F. A. M.

BOLAND, F. K.: *Celebration of the Centennial of Anesthesia at the Massachusetts General Hospital.* J. M. A. Georgia **35**: 294–296 (Oct.) 1946.

"The Massachusetts General Hospital has sent out invitations to the celebration of the centennial of the first public demonstration of surgical anesthesia in that venerable institution, October 16, 1846. . . . This event is typical of the activities of this Massachusetts hospital in keeping alive the memory of Morton's administration of ether one hundred years ago. . . . How I wish Georgia doctors would become this enthusiastic over the real first anesthetic, that given by a Georgia doctor in Jefferson, Georgia, March 30, 1842, four and one half years before Morton gave his first anesthetic. We commemorate Crawford Long Day in Athens every 30th day of March, and all members of the Medical Association of Georgia know about it and are invited to it, but it is a rare thing ever to see as many as a half dozen doctors present. We congratulate the Massachusetts General Hospital upon this historic occasion, and wish for it the greatest success, and a long continuation of similar celebrations."

F. A. M.